Author's response to reviews

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

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Version: 5 Date: 2 December 2005

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: 3 Date: 24 September 2005
Reviewer: James Zacny

Reviewer’s report: General

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

1. I noted in a prior study by the authors published in the same journal that an abstract was included. The version I was asked to review did not have an abstract.  
   An abstract is included in this version of the manuscript.

2. The study was well-designed and the results appear to be valid, and the authors produced a well-written paper. However, this reviewer is unclear as to whether this study informs on predictors of prescription opioid abuse in a chronic pain population. This would be extremely valuable information to have. It seems like the authors wanted to address this issue: see p. 2, lines 18-20, and parts of the 2nd and 3rd paragraphs of the Discussion section. For example on p. 2, the authors state specifically generalists are said to worry about misuse and diversion of prescription opioids. But the study was apparently designed to focus on substance abuse in general. So from the results we know that predictors of substance abuse include history of cocaine abuse, alcohol abuse, and previous drug or DUI conviction or multiple drug convictions, and age. Does this tell a primary care physician anything about potential red flags indicating possible diversion or abuse of prescription opioids? This reviewer believes the answer is “no.” What this reviewer would like, but does not know if it is possible, is to focus on those patients who showed evidence of prescription opioid abuse (and call them the “users”) and re-run the bivariate and multivariate statistical analysis. Perhaps the same results would occur….that patients who had problems with prescription opioids (as explicitly defined on pp. 5 and 6) had histories of cocaine and alcohol abuse and had convictions, etc. But perhaps not. A study by Dunbar and Katz (Journal of Pain and Symptom Management, 11:163-171) showed that prior alcohol abuse was not a predictor of prescription opioid abuse. Chabal et al. (Clin J Pain, 1997 13:150-155) reported that past opiate or alcohol abuse failed to be predictors of prescription opioid abuse. The present study is a good study but it could have been more informative to doctors who are concerned about prescription opioid abuse amongst their patients if they focused on prescription opioid misuse and not substance misuse in general. This reviewer believes this needs to be added as a caveat to the study. Also the 2nd and 3rd paragraphs of the Discussion section are a bit confusing because both substance abuse and opioid abuse are discussed as if they are the same thing.

Overall, the manuscript has been clarified to focus upon opioid misuse, including an analysis of those study patients with only 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 pre-defined endpoint of interest. We do provide these tables below.

Further, the terminology has been changed for the sake of clarity Of note, both reviewers of have questioned our term “substance misuse” and have suggested that the conventional terms substance abuse, dependence and addiction are more appropriate.
As we were developing our pain management program and grappling with what would constitute violations of our medication agreement, we realized that substance abuse and addiction were not necessarily applicable to our setting and circumstances. For instance, as an academic internal medicine clinic with many different providers and many learners, we had neither the resources nor, strictly speaking, the expertise to make confident and consistent diagnoses of addiction. In addition, we identified behaviors that, though aberrant and inappropriate, would not necessarily be encompassed by these terms. Prescription forgery comes immediately to mind. Does this constitute prima facie evidence of addiction or substance abuse? The patient could be diverting.

This definitional dilemma became more salient due to our reliance on urine toxicology. As we were developing a working diagnosis of substance misuse, we were surprised by the frequency of patients with urines negative for methadone and morphine (on multiple occasions) that should have been positive given the amount of tablets provided and the history of ingestion. (Frankly we had not anticipated this. In the program development phase, we were initially obtaining tox screens to assess for cocaine and amphetamine use.) Patients were informed in the medication agreement that urinary evidence of prescription opioid use would be a precondition for ongoing opioid provision. Many of these patients would not have aroused suspicion as either addicts or substance abusers on clinical grounds. Our best surmise is that these patients were diverting these medications or possibly substituting a different urine. We chose to label this finding as misuse in order to distinguish it from abuse, dependence and addiction because the patients ostensibly did not meet criteria for these entities, and we were not in a position to either formally evaluate for abuse, dependence and addiction, or prove diversion. In addition, we felt that it would be unfair to label some patients as either addicts or abusers if we could not establish it with reasonable certainty.

Our definition simply derives from the stipulations of the medication agreement which is similar to agreements in common use. Some of our patients were undoubtedly abusers and addicts, but the primary objective of our program was to manage pain while at the same time mitigating substance misuse (especially the possibility of diversion). We believe that our definition of substance misuse is a pragmatic one that can easily be used in general practice settings where chronic pain is treated but where psychiatric and psychological support is not readily available to formally evaluate patients for substance abuse and addiction (which is the case at our institution). It allows for a straightforward and consistent approach to the problem within a given practice.

Thank you for the new reference.

**Bivariate Analysis: Predictors of Opioid Misuse**

<table>
<thead>
<tr>
<th></th>
<th>Non-Misusers</th>
<th>Misusers</th>
<th>p-value</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.9</td>
<td>46.1</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>% Male</td>
<td>38.1</td>
<td>59.5</td>
<td>0.020</td>
<td>1.97 (1.10-3.52)</td>
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<tr>
<td>% Positive Urine Cannabinoids</td>
<td>16.3</td>
<td>46.7</td>
<td>0.0002</td>
<td>2.87 (1.68-4.88)</td>
</tr>
<tr>
<td>% History of Cocaine Abuse</td>
<td>15.5</td>
<td>47.8</td>
<td>0.0010</td>
<td>3.10 (1.60-5.96)</td>
</tr>
<tr>
<td>% History of Ethanol Abuse</td>
<td>15.8</td>
<td>34.1</td>
<td>0.0106</td>
<td>2.15 (1.20-3.85)</td>
</tr>
<tr>
<td>% Current Smoker</td>
<td>50.4</td>
<td>67.6</td>
<td>0.067</td>
<td>1.34 (1.013-1.78)</td>
</tr>
<tr>
<td>% Multidrug Convictions</td>
<td>20.4</td>
<td>75.0</td>
<td>0.0087</td>
<td>3.68 (1.94-6.99)</td>
</tr>
</tbody>
</table>
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Background, line 8-11: this sentence probably should be modified. It implies that as a result of the recent increase in prescription drug diversion, 28 states have enacted prescription monitoring programs (PMPs). A number of states have had PMPs for many years (see Journal of Pain and Symptom Management, volume 23:231-238).

Information provided on this issue has been updated and clarified.

2. Page 3, lines 1-3: again this sentence should probably be modified. At least to this reviewer it implies references 21-26 all deal with studies in patients who were receiving substance abuse treatment. Reference 25 was not a study but a conceptual issues paper. I am not sure of the relevance of Ref 26, as this was a study done in chronic pain patients in a primary care setting (perhaps some of the patients had histories of substance abuse but that was not an inclusion criterion to study entry).

The sentence has been modified. We discovered that several references were out of place, and this has been corrected. Thank you for noticing this.

3. I am not sure where to put this comment, but I will place it here. Page 7: were patients asked whether they had abused prescription opioids or heroin? Were they only asked whether they abused cocaine? This reviewer would think that a past or current history of heroin use or a past history of prescription opioids would predict substance misuse during the 1-year prospective study.
These questions were asked to study participants. This point has been clarified.

4. Discussion, page 12, lines 6,7: the authors state that the pattern of substance abuse in their population often suggested polysubstance abuse. Can the authors provide some data to back up this claim?
This point has also been clarified.

5. P. 10, line 13: typo. Instead of “predicted substance misuse” should be “predictor of substance misuse.”
The typo has been corrected.

6. p. 14, lines 13-16: Can the authors elaborate on what are the restrictive new DEA regulations with regard to the provision of Schedule II opioids? This is a strong statement to make, and I am not convinced the DEA is doing anything to prevent the supply of such drugs as morphine and oxycodone to doctors and patients. Also the authors make an assertion that needs some

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Cocaine Abuse</td>
<td>2.44</td>
<td>0.141</td>
</tr>
<tr>
<td>History of Alcohol Abuse</td>
<td>4.11</td>
<td>0.014</td>
</tr>
<tr>
<td>Age</td>
<td>0.91</td>
<td>0.009</td>
</tr>
<tr>
<td>Drug or DUI Conviction</td>
<td>1.30</td>
<td>0.693</td>
</tr>
</tbody>
</table>
references: is it indeed true based on survey data that physicians are reluctant to prescribe opioids? And is it due to the DEA’s apparent actions and reporting of high profile cases of prosecution of pain-treating physicians? The sentence appears to be conjecture. It is not clear whether smoking was used in the bivariate and multivariate analyses. A study by Michna et al. (JPSM, 28:250-258) indicated that chronic pain patients who displayed aberrant drug behavior were more likely to be smokers.

The tone of this section has been tempered in a more objective manner. References have been changed to mirror this refocus. The issue of tobacco smoking was considered, but did not reach significance.

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Discretionary Revisions (which the author can choose to ignore)

What next? Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests: I declare that I have no competing interests.
Reviewer's report
Title: Predictors of Substance Misuse in Patients with Chronic Pain, A Prospective Cohort Study
Version: 4 Date: 9 November 2005
Reviewer: David A Fiellin
Reviewer's report: General

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

Specific remarks
Introduction: No comments.

Methods
Pg. 4, line 5. All patients were referred. Referral bias should be discussed as a limitation.
As stated in the manuscript (same section), as physicians were encouraged, not mandated, to refer patients.

Pg. 4, line 9. This was a resource intensive team. Generalizability needs to be considered
This was discussed in the Discussion section. We will point out, however, that we are billing for our pain services using mid-level providers and that such an arrangement is potentially financially sustainable.

Pg. 4, line 10 and 11. Were non-pharmacologic treatments considered, used?
Other modalities were used, and this has been added to the manuscript.

Pg. 6, line 26. Define “regular basis”.
This has been changed to those who were seeing multiple providers concurrently. We wanted to emphasize that episodic use of the emergency room or urgent for legitimate exacerbations of pain would not be viewed as “doctor shopping” in and of itself.

Results
Pg. 9, line 2. 196 participated, how many were referred?
As noted in the rest of that sentence, a total of 199 were referred.

Pg. 9, line 10. We still do not know the relative prevalence of misusers.
This is discussed in succeeding paragraphs.

Pg. 11, line 1-6. The presentation on UTS + for cannabinoids is not warranted given that this did not remain in the multivariable model. This section should be deleted.
This entire section has been altered.

Pg. 12, line 7. The definition of “polysubstance abuse” should be avoided. This term should be reserved for drug users who are dependent on a number of different types of substances. Instead, multiple co-morbid diagnoses of Substance Abuse or Dependence (one for each class that the person is dependent on) should be given if appropriate. I do not believe the authors have enough information to make this determination.
As noted above, the terminology has been changed throughout the entire manuscript.

The authors should provide details on the case management and an assessment of the potential impact of case management on the outcomes of interest (substance use disorders)?
This issue is discussed in the Methods section.
Discussion

Pg. 12, line 19-21. The authors need to be cautious about their use of misuse and addiction. Throughout the manuscript they should stick to the DSM-IV terms of abuse and dependence given that these have operational definitions.

The terminology has been changed for the sake of clarity. Of note, both reviewers of have questioned our term “substance misuse” and have suggested that the conventional terms substance abuse, dependence and addiction are more appropriate.

As we were developing our pain management program and grappling with what would constitute violations of our medication agreement, we realized that substance abuse and addiction were not necessarily applicable to our setting and circumstances. For instance, as an academic internal medicine clinic with many different providers and many learners, we had neither the resources nor, strictly speaking, the expertise to make confident and consistent diagnoses of addiction. In addition, we identified behaviors that, though aberrant and inappropriate, would not necessarily be encompassed by these terms. Prescription forgery comes immediately to mind. Does this constitute prima facie evidence of addiction or substance abuse? The patient could be diverting.

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Pg. 14, line 9-11. The authors provide no detail in the manuscript that they have treated pain effectively and compassionately. This point has been referenced which describes our pain management process in greater detail.

Pg. 14. The following limitations should be addressed:
No formal SCID or DSM-IV diagnoses for substance abuse or dependence were performed on patients. Specifically noted in the paragraph on limitations. The authors used a proprietary and non-validated definition of misuse and addiction. This has been addressed in the fifth paragraph of the Discussion section (See discussion above.) The data on drug offenses and DUI are not usually available to clinicians. This has been noted. The monitoring may not have been performed frequently enough to assess substance use disorders including abuse. This point may be true, but it is impossible to continuously assess for this in a general medicine practice.

Conclusion
Pg. 16, line 4-5. Provide references to other studies that provide reasonable estimates of prevalence. This has been done.

Tables: No comments.

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

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 outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No
Declaration of competing interests: 'I declare that I have no competing interests'