Author's response to reviews

Title: A primary care, multi-disciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric co-morbidity

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Author's response to reviews: see over
Response to Reviewers Report: **Development and testing of a primary care disease management program for patients with chronic pain**

**To The Editors of BMC Central:**

We have completed the revisions of our manuscript requested by the reviewers. Notably, we have changed the title of the manuscript and made it more reflective of the population we studied. Below, you will find a point-by-point response to the reviewers’ reports.

Sincerely,

Paul Roman Chelminski, MD, MPH

**Reviewer:** Andrew Cook

**Major Revisions**

1. The study would be strengthened by editing of the title, abstract, introduction and discussion to more closely reflect the design and sample employed…

We have modified our title to better reflect the population studied in our program. The title is now: **A primary care, multi-disciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric co-morbidity**

2. More information is needed on lost subjects given that 15/22 of these were due to discontinuation of opioids…

As recommended we have furnished comparative data in table format for those patients identified with substance misuse who did not complete the trial. These results are discussed on page 12 under Substance Misuse and are presented in Table 6 in the revised document (page 21). This table compares baseline characteristics of patients who completed the trial and those who committed substance misuse and did not complete the trial. Comparison of these two groups demonstrates a trend toward a higher degree of depression among the substance misusers.

3. In reference to #2, the comparison of % prevalence of depression pre- and posttreatment (table3, line 7) may not be meaningful.

As noted in the revisions in #2 above, there was a higher prevalence of depression among substance misusers who dropped out before three month follow up was higher. This might lead to overestimation of the effect of the intervention. This limitation is acknowledged in the discussion.

4. a. More attention in the discussion to the limitations on replication/generalization due to individualization of treatment…

We acknowledge that our intervention was individualized. We did not adhere to strict algorithms for diagnosis and treatment. The evidence-base to manage chronic pain in the
general internal medicine setting is limited and the patient population is challenging. As such, we decided to allow more latitude and individualization in treatment choice. We have subsequently developed more robust algorithms and will make them available over the Internet so that others can benefit from our experience.

b. Also the use of a committee for defining and/or acting on misuse highlights the subjective component of these determinations: can your decision rules be more explicitly stated or are there suggestions for greater standardization in future studies?

We developed our definition of substance misuse to minimize subjective determinations. Contrary to usual clinical practice, we did not define substance misuse through individualized or arbitrary decisions. We instead developed a pre-defined and relatively unambiguous definition of substance misuse, which we applied prospectively and uniformly to all participants. Our definition is stated explicitly on page 8, paragraph 1. We believe that this definition is practical and could be adopted by other primary care practices.

5. Because of common overlap in symptoms of chronic pain and depression (particularly neurovegetative components), it is generally recommended that adjusted cut-offs be used with standardized depression scales such as the CES-D, to improve specificity...

We are grateful to the reviewer for supplying the reference by Geisser et al. We have rerun our analyses using a higher CESD threshold for diagnosing depression in chronic pain patients and the incorporated these results into the manuscript (page 11, para 1, and Table 3, page 20).

6. Were the research assistants who conducted post-treatment assessments blind to the re-treatment assessments or were these conducted by the same people?

There was no blinding of research assistants. We acknowledge this in the limitations.

7. a. The high prevalence of substance misuse is a very important finding, and would be central in many readers’ evaluations of the feasibility and value of this type of program...

We agree that the finding of substance misuse is an important finding of this research. The magnitude of the substance problem surprised many of us. We studied a population referred specifically for potential problems with pain management, including suspicion of substance misuse. As such, we cannot generalize about the prevalence of substance misuse in the larger population of patients with chronic pain. A more extensive analysis of substance misuse in our population is the subject of a separate manuscript that focuses on an expanded sample of patients enrolled in our program.
b. If most patients decline substance abuse referrals, how else can they be treated to avoid the common migration between clinics/providers?

With regard to migration of patients, our program implemented policies to prevent migration of patient within our practice. The cornerstone of these policies was meticulous documentation in the electronic medical record. We have no direct control over migration that occurs outside of our practice and our health care system.

8. The alpha (type I) error rate should be controlled for the multiple statistical comparisons...

In our manuscript, we examine several outcomes, including pain, disability, and depression. However, because each outcome is only considered individually and is not used to make an inference about the overall effectiveness of the program, adjustment for multiple comparisons is not warranted.

9. Given the uncontrolled design, the potential impact of non-specific treatment effects (placebo) needs to be addressed in the discussion...

We acknowledge in the discussion that non-treatment effects could influence outcomes and that our study design did not control for this potential effect.

Minor Revisions
10. The sample contract, referred to as appendix A, is missing.

We have added the sample contract to the end of the manuscript (page 28).

11. Please elaborate on how psychiatric comorbidity was diagnosed (p. 7, lines 5-8). Was this based on clinical interview or were screening tests used?

To diagnose depression, we used a combination of clinical interview and CESD (page 7, lines 17-18).

12. The finding of no demonstrated benefit from substantial increases in opioid doses has significant clinical implications. Recommend greater attention to this finding in the discussion.

We have chosen not to emphasize this finding more because the study design was not sufficiently rigorous to draw valid inferences from the available data.

13. Polysubstance abuse was often suspected (p.15, line 5). How might this have affected treatment response?

We do not know the effect of substance misuse on treatment efficacy, other than the high withdrawal rate from treatment after detection of substance misuse, which would presumably lead to poorer outcomes in the subjects who leave treatment, both for pain
and for depression. We are devoting more attention to the substance misuse issues in a separate manuscript.

14. The full name of the CES-D is Center for Epidemiological Studies – Depression Scale (p.2, line12 and other points in manuscript).

We have clarified the name of the Center for Epidemiological Studies-Depression Scale on page 2 and then employed the abbreviation CESD in the remainder of the text.

**Discretionary Revisions**
15. Were data on past substance abuse/misuse analyzed as potential predictors of treatment response, substance misuse and/or dropout?

This is the focus of a separate manuscript.

**Reviewer 2: Bill H McCarberg**

**Major Compulsory Revisions**
1. Page 12 line 11 mentions "neuropathic blockers". There are no such drugs. A different phrase should be used.

Neuropathic blockers has been removed and terminology changed to “adjunctive analgesics.”

2. I suggest an explanation on the outcome measures BPI, CESD and PDI on what is considered mild, moderate or severe...

We have provided explanations for the scores used as footnotes to Table 3 (page 20).

3. This population is very distinct, 60% male (most chronic noncancer pain studies show a predominance of females), 87% smokers...

We agree that this is a selected group of patients within our practice. We do not have information beyond the descriptive information already presented.

4. Page 6 line 9 mentions the "Medication Contract". Some mention should be made that "contract" is not what the pain experts recommend. Medication Agreement, Informed Consent is more appropriate.

We are aware that Medication Agreement has supplanted Medication Contract as the conventional terminology. Our study used the term Medication Contract but we have since switched in practice to Medication Agreement.

**Minor Essential Revisions**
1. Please use the word chronic noncancer pain, not non-malignant pain...
The change has been made.

2. Page 3 line 16 uses reference 16 for opioids in non-malignant pain. This reference is for the treatment of metastatic cancer, not non-malignant pain...

The reference has been inserted in its proper place in the text (page 3, paragraph 2).

3. Page 4 line 11 - "fostering opioid dependence, abuse or addiction". I do not understand this statement, addiction and abuse are the same; physical dependence always happens with an opioid used longterm and is not abuse. Why are these terms used together?

We have modified this sentence and substituted misuse for abuse (page 4, paragraph 2). Primary care physicians are generally not in a position to make unambiguous determinations of addiction. We have used the term misuse to denote a set of objective behaviors that indicate inappropriate uses of opioids.

4. Page 4 line 16 states that "Traditional models of office-based care focus on diagnoses and acute management of medical problems..."

We acknowledge that many of these characteristics may be used in conventional outpatient practices, and it is true that some practices have adopted multi-disciplinary approaches. But many independent practices have not. Our program is distinguished by applying disease management principles in an intensive, structured, coordinated manner. We have amended the text to reflect this.

5. Page 6 line 15: guidelines. Only the last reference is a guideline. The others are author’s opinions.

We have added “expert opinion” to justify the references used (page 7, line 2).

6. Page 6 line 23: less costly, generic medications. This is not a basic principle (misspelled in text) of management. It is a necessity in managed care...

We believe that using less costly medications is an essential element of care, especially when the more expensive, proprietary medications have not been shown to have greater efficacy. Managed care has never been a strong force in North Carolina. Many of our patients receive their medication through a state-subsidized pharmacy benefit at the hospital. Oxycontin®, for example, is 10 times more expensive to the hospital than methadone. No changes made except correction of the spelling of “principle.”

7. Page 7 line 1: gabapentin does not work in chronic pain; it works in a few types of neuropathic pain.

We used gabapentin for neuropathic pain. We have removed “known efficacy in chronic pain” (page 7, lines 8-11).
8. Page 10 line 21: if there was intense monitoring and psychosocial evaluation of the patients, why did the percent of patient on anti-depressants increase from 44% to only 52% after 3 months?

We did not have a structured treatment algorithm for depression and but have since added one. We have clarified the text in the Discussion to reflect this (page 14, lines 2-4).

9. The Hawthorne effect should be explained.

We have elaborated on the Hawthorne effect in the limitations paragraph (page 17, paragraph 1).

10. Page 13 line 22: "not lost or stolen medication" is not correctly worded. Should read: and not addiction.

This change has been made (pages 14-15, starting on last paragraph of page 14).

**Discretionary Revisions**

We appreciate the author’s observations on the quandaries of managing chronic, non-cancer pain. These are issues that we struggle with continually. The substance misuse issues (including the risks of prescribing opioids) are especially compelling and are the subject of a separate manuscript on an expanded sample of patients enrolled in our program.