Reviewer's report

Title: Clinical evaluation of the efficacy of methylnaltrexone in resolving constipation induced by different opioid subtypes combined with laboratory analysis of immunomodulatory and antiangiogenic effects of methylnaltrexone

Version: 4 Date: 9 May 2014

Reviewer: Katherine Clark

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1. Will the study design adequately test the hypothesis?
There is no null hypothesis given and I think that this is an oversight that should be corrected.

The primary aim of the study is to compare the efficacy of methylnaltrexone to induce laxation when people are receiving specific opioids. At present, this is listed as an objective. This should be corrected.

Expanding on this, the aims of the study need to be included in the abstract.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?
In the current form, I think that there are problems with the study that need to be addressed before this work could be easily replicated.

Firstly, there is not a clear definition of what problems people have to be experiencing before they enter the study? I acknowledge that there is no agreed definition of opioid-induced constipation but it seems to me that it is impossible to understand without a clear outline of the problems that people are experiencing at baseline, how changes can be tracked? This is highlighted that the authors have suggested that bowel actions occurring less frequently than 3rd daily is representative of problems; it must be noted that this is the usual pattern for many people.

This is highlighted by the fact that no objective inclusion criteria listed for the study? I note the BFI is being tracked; could this not be used as inclusion criteria?

This brings me to the next point. I am concerned that the exclusion criteria are not comprehensive enough. There is no mention of renal function, pregnancy or hydration status. Given the association of methylnaltrexone with excessive sweating, I think failing to assess hydration status is a major oversight.

Additionally, the exclusion criteria highlight that people will be excluded if there is a more probable cause of constipation defined? How will this all be objectively qualified?

I am not sure how adverse events are being quantified? Should not specific problems related to methylnaltrexone be monitored and graded? Clearer stopping rules are needed.
Further, people are asked to keep a bowel diary; what does this measure and why?

3. Does the manuscript adhere to the relevant standards for reporting and data deposition: if not, in what ways?
   As above, I think that clearer criteria are needed to best report the work.
   There is no mention made of demographic data.

4. Is the writing acceptable?
   I have some concerns regarding the introductory section of the paper.
   In the opening sentence the prevalence of constipation is quoted as between 30-50%. Other papers have quoted much higher rates than this in palliative care. Due to the lack of agreed criteria in this space, I think such figures need to be clarified.
   Is there a reference for the suggestion that constipation causes nausea?
   Gastroenterologists define constipation as either a problem of slow colon transit or a disorder of the pelvic floor. I note the definition given here (without a reference) is that constipation is due to mechanical obstructions or impaired gut motility?
   Furthermore, there is a statement that opioids often cause impaired gut motility. What reference is there to support this in this specific population?