PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Hypogonadism and low bone mineral density in patients on long-term intrathecal opioid delivery therapy
AUTHORS	Duarte, Rui; Raphael, Jon; Southall, Jane; Labib, Mourad; Whallett, Andrew; Ashford, Robert

VERSION 1 - REVIEW

REVIEWER	Dr. Simon Thomson MBBS FFPMRCA Consultant in pain medicine and neuromodulation Basildon and Thurrock University Hospitals United Kingdom
REVIEW RETURNED	17-Mar-2013

GENERAL COMMENTS	I believe that this paper could be published as it is. Your data and discussion focusses quite correctly on the research question and you do not stray from that brief. Nice work and well presented! If other reviewers request a minor revision then please consider the following. However I am left wanting more discussion for the future. There are just two areas of a missed opportunity: 1 You have not reported upon the sexual health of the participants. For example the correlation between FT and SHBG and libido in these patients. To the practitioner a routine screening of sexual libido may help the decision as to perform annual endocrine screen and replacement therapy. On the other hand low BMD associated with low FT is so common that perhaps routine annual screening is required, but I wonder if there are more identifiable clinical risk factors. 2. Have you any recommendations for future study so as to elucidate for example whether the reduced FT and BMD is more prevalent in IT Morphine versus, IT Ziconotide or versus long term oral opioids. Perhaps SCS patients could be a control group.

REVIEWER	Dr. Stan Van Uum, Dept. of Medicine, Western University, London, Ontario, Canada.
REVIEW RETURNED	26-Mar-2013

THE STUDY	Exclusion criteria need to be clarified.
REPORTING & ETHICS	Please clarify if the Research Ethics Board approved the study? Was informed consent required, and if yes, obtained?
GENERAL COMMENTS	In this study the authors investigate the presence of hypogonadism and decreased bone density in patients treated with long term intrathecal opioids. The authors study 20 patients and finds central hypogonadism in most of these patients, and a high prevalence of

	decreased bone mineral density. I agree with the authors that there is a dearth of information on this topic, and this study provides new information. However, there are several items I would like to see addressed: **Major** o Methods page 4 – please describe if there were any exclusion criteria in addition to the testosterone treatment within 3 months? Further, please clarify if the study was approved by the Research Ethics Board, and was informed consent required and, if so, obtained? o Result section: please start with a paragraph describing the subjects. Were any patients excluded from inclusion? If so, why? o Page 5, line 17 – please clarify the time of the day when the blood samples were taken. In general, guidelines advise to take blood samples for testosterone in the early morning because of the diurnal rhythm o Page 7, lines 37-39. The presence of biochemical hypogonadism was determined using free testosterone levels. Please also provide information on the presence of biochemical hypogonadism as diagnosed based on total testosterone levels. o Page 8, table 2: Regarding the BMD assessment, please clarify if all participants were Caucasian and if not, if the BMD score was based on scores for ethnicity specific reference values? **Minor** o Page 7, table 1: please provide information on BMI in this table. o Page 7, Table 1: please clarify if prolactin levels were measured to rule out hyperprolactinaemia as an alternative cause of central hypogonadism. o Page 7-8: please clarify if any X-rays were done to look for osteoporosis related fractures (which could also affect BMD measurement). o Page 11, last paragraph, lines 47-48: as gonadal status and BMD were not determined before inclusion in this study, I suggest that the authors state that this study can not conclude that the decreased BMD is caused by the hypogonadism. o Page 12, lines 10-16. To my knowledge, the effect of hormone replacement of hypogonadism has not been explicitly studied in patients with opioid induced hypogonadism. Could the authors please comment on this and the potential need for further studies in this patient group?

REVIEWER	Eldabe, Sam South Tees NHS Trust
REVIEW RETURNED	29-Mar-2013

REPORTING & ETHICS	The data for this observational study appears to have been collected under clinical care not as a study no consenting was mentioned in the manuscript
GENERAL COMMENTS	This is a useful observational study of a small number of patients undergoing intrathecal therapy. The conclusions are appropriate as the authors can only point to a possible association with osteoporosis given the small numbers no firm conclusions can be drawn. It would be useful to know how many of the patients included were also receiving systemic opioids. The study would have come to much stronger conclusions about the causation had the authors compared their subjects to a matched cohort of chronic pain patients.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Dr. Simon Thomson MBBS FFPMRCA
Consultant in pain medicine and neuromodulation
Basildon and Thurrock University Hospitals
United Kingdom

I believe that this paper could be published as it is. Your data and discussion focusses quite correctly on the research question and you do not stray from that brief. Nice work and well presented!
If other reviewers request a minor revision then please consider the following.

However I am left wanting more discussion for the future.
There are just two areas of a missed opportunity:
1 You have not reported upon the sexual health of the participants. For example the correlation between FT and SHBG and libido in these patients. To the practitioner a routine screening of sexual libido may help the decision as to perform annual endocrine screen and replacement therapy. On the other hand low BMD associated with low FT is so common that perhaps routine annual screening is required, but I wonder if there are more identifiable clinical risk factors.
2. Have you any recommendations for future study so as to elucidate for example whether the reduced FT and BMD is more prevalent in IT Morphine versus, IT Ziconotide or versus long term oral opioids. Perhaps SCS patients could be a control group.
Response: Thank you, we have now included recommendations for future studies, including sexual health in the penultimate paragraph.

Reviewer: Dr. Stan Van Uum, Dept. of Medicine, Western University, London, Ontario, Canada.

REVIEW BMJOpen March 2013

Review by Dr. Stan Van Uum, Dept. of Medicine, Western University, London, Ontario, Canada.

Title: Hypogonadism and low bone mineral density in patients on long-term intrathecal opioid delivery treatment.

In this study the authors investigate the presence of hypogonadism and decreased bone density in patients treated with long term intrathecal opioids. The authors study 20 patients and finds central hypogonadism in most of these patients, and a high prevalence of decreased bone mineral density.
I agree with the authors that there is a dearth of information on this topic, and this study provides new

information. However, there are several items I would like to see addressed:

Major
o Methods page 4 – please describe if there were any exclusion criteria in addition to the testosterone treatment within 3 months? Further, please clarify if the study was approved by the Research Ethics Board, and was informed consent required and, if so, obtained?
Response: Testosterone treatment was the only exclusion criteria, however, none of the patients was receiving hormonal replacement therapy and therefore there were no exclusions. We included that sentence to inform the reader that this had been considered. In Methods/Patients, we have reworded the exclusion criteria sentence to the following: “None of these patients received testosterone supplementation within the previous three months.”
Regarding ethical approval and informed consent, in this centre intrathecal opioid patients are screened on a yearly basis for hormonal levels as part of routine clinical care. BMD assessment is part of routine clinical care for hypogonadal patients, hence the reason why DEXA was only performed in hypogonadal patients. We have now added to Methods/Patients section the sentences: “All assessments were performed as part of routine clinical care. No additional procedures were carried out for research purposes.”

o Result section: please start with a paragraph describing the subjects. Were any patients excluded from inclusion? If so, why?
Response: No patients were excluded and we have now stated this in the Methods/Patients section. Due to the structure of the paper and different assessments with different number of participants, we though it would be clearer to describe the 20 participants of the study in the Methods/Patients section and then in the respective results section (Assessment of Sex Hormones and Assessment of Bone Mineral Density). We agree that had any patients been excluded we should have started the results section with that information.

o Page 5, line 17 – please clarify the time of the day when the blood samples were taken. In general, guidelines advise to take blood samples for testosterone in the early morning because of the diurnal rhythm
Response: Thank you for noticing this. We have now included the time of the day when the blood samples were taken in page 5. “Blood samples were collected between 8am and 11am…”

o Page 7, lines 37-39. The presence of biochemical hypogonadism was determined using free testosterone levels. Please also provide information on the presence of biochemical hypogonadism as diagnosed based on total testosterone levels.
Response: This has now been included in page 7.

o Page 8, table 2: Regarding the BMD assessment, please clarify if all participants were Caucasian and if not, if the BMD score was based on scores for ethnicity specific reference values?
Response: All the participants were Caucasian. This has now been clarified in the second paragraph of page 8.

Minor
o Page 7, table 1: please provide information on BMI in this table.
Response: We would prefer to have the BMI information presented in “Assessment of Bone Mineral Density” section and not in Table 1 as BMI was not collected for all participants, but only for those who had a DEXA scan.

o Page 7, Table 1: please clarify if prolactin levels were measured to rule out hyperprolactinaemia as an alternative cause of central hypogonadism.
Response: Thank you, prolactin was measured (added to the Methods section), results of prolactin

levels were now included in Table 1 and are also discussed.

o Page 7-8: please clarify if any X-rays were done to look for osteoporosis related fractures (which could also affect BMD measurement).
Response: We have now clarified in page 9 that investigation of osteoporosis related fractures through x-rays were not performed.

o Page 11, last paragraph, lines 47-48: as gonadal status and BMD were not determined before inclusion in this study, I suggest that the authors state that this study can not conclude that the decreased BMD is caused by the hypogonadism.
Response: The following sentence has been added to the final paragraph: “However, since the gonadal status and BMD were not determined prior to initiation of intrathecal opioid delivery, we cannot conclude that the decreased BMD was caused by hypogonadism or opioid administration.”

o Page 12, lines 10-16. To my knowledge, the effect of hormone replacement of hypogonadism has not been explicitly studied in patients with opioid induced hypogonadism. Could the authors please comment on this and the potential need for further studies in this patient group?
Response: We have now added information on page 13 of studies investigating the effect of hormone replacement therapy in opioid induced hypogonadism patients.

Reviewer: Sam Eldabe
South Tees NHS Trust

This is a useful observational study of a small number of patients undergoing intrathecal therapy. The conclusions are appropriate as the authors can only point to a possible association with osteoporosis given the small numbers no firm conclusions can be drawn.

It would be useful to know how many of the patients included were also receiving systemic opioids.
Response: Information on systemic opioids was not collected. We have now acknowledged this in the study limitations. “Information on systemic opioids was not collected. A proportion of these patients are provided with oral opioid medication on an individual basis for occasional flare-ups. The strongest systemic opioid provided is tramadol at a dose ≤ 400 mg/day.”

The study would have come to much stronger conclusions about the causation had the authors compared their subjects to a matched cohort of chronic pain patients, can the authors explain why they did not pursue that
Response: We agree with the reviewer that a comparative study would allow stronger conclusions. A comparative study was not carried out at this time as we were only analyzing data routinely collected in our cohort of patients. We have now included recommendations for future studies in the penultimate paragraph.

VERSION 2 – REVIEW

REVIEWER	Stan Van Uum, Dept. of Medicine, Western University London, Ontario Canada
REVIEW RETURNED	03-May-2013

THE STUDY	For an ideal study, htere should be an adequate control group. However, given the pilot character of this study, the result are still quite relevant

GENERAL COMMENTS	This paper has significantly improved. I have two suggestions for the authors: 1) Please delete the reference ranges in the methods section, and in stead present them in Table 1 - this will make it easier for the readers to interpret the results. 2) The second paragraph of the discussion relates to sexual function in this patient group. While this is a very relevant topic for this patient group, the present study does not assess sexual function. Therefore, I would suggest so shorten this paragraph and move this to the limitations section of the paper.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Stan Van Uum,
Dept. of Medicine, Western University
London, Ontario
Canada

For an ideal study, there should be an adequate control group. However, given the pilot character of this study, the result are still quite relevant

This paper has significantly improved. I have two suggestions for the authors:

1) Please delete the reference ranges in the methods section, and in stead present them in Table 1 - this will make it easier for the readers to interpret the results.
Response: We agree with Dr Van Uum and have deleted the reference ranges from the methods section and presented them in Table 1.

2) The second paragraph of the discussion relates to sexual function in this patient group. While this is a very relevant topic for this patient group, the present study does not assess sexual function. Therefore, I would suggest so shorten this paragraph and move this to the limitations section of the paper.
Response: We have now shortened this paragraph and moved it to the limitations section of the paper.