

August 1st,
2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4020-review.docx).

Title: Pharmacological pain management in chronic pancreatitis

Authors: Søren S. Olesen, Jacob Juel, Carina Graversen, Yuri Kolesnikov, Oliver H.G. Wilder-Smith, Asbjørn M. Drewes

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4020

The manuscript has been improved according to the suggestions of reviewers and changes highlighted in yellow:

1. Format has been updated according to journal guidelines.
2. Revision has been made according to the suggestions of the reviewers:
 - (1) The reviewer wrote: "The language can be polished to make the article more confluent and concrete."
Our reply: Dr. Oliver H.G. Wilder-Smith, who is a native speaking Englishman with vast experience in scientific English, has revised the language of the manuscript and we consider the language of the paper as Grade A. Hence, no further language revision by external sources is by our opinion needed.
 - (2) The reviewer wrote: "...in the second paragraph of part "Overview of pain mechanisms in CP", the author writes: "Furthermore, the experimental evidence supporting this theory is sparse and findings have been conflicting". If there can be further descriptions about the conflictions mentioned above, that will be better."
Our reply: "We agree that the mechanisms underlying pain in chronic pancreatitis should be more detailed described. However, this information is provided in a separate review article in the current top highlight of the journal. This has been clarified in the manuscript and the paragraph reads "A detailed overview of the complex pain mechanisms underlying pain in CP is beyond the scope of this review and provided elsewhere in this issue of the journal."
 - (3) The reviewer wrote: "...dosages are supposed to be given everytime a new treatment cited for further reference."
Our reply: We agree and whenever possible the treatment dosage is provided in the manuscript. However, for some treatments an exact dosing regime cannot be

given for the individual patient. For example, many different opioids exist with a different potency and side effect profile. Hence, an individual titration is essential in each patient in order to ensure a favorable analgesic outcome along with acceptable side effects. Also, for more experimental treatments such as antioxidants, many different “antioxidant mixtures” exist and it is not feasible to list the dosage regime for all of them.

- (4) The reviewer wrote: “...at the final of the article, the author mentioned that “Analgesics are typically titrated according to the WHO ladder principle, but in some situations a top-down approach may be useful to control pain and avoid sensitization of central pain pathways”, while the top-down approach hasn’t been clearly reviewed in this article.

Our reply: We agree with this point and the top-down approach has now been explained in the text reading: “The standard guideline for analgesic therapy in CP patients follows the principles of the “pain relief ladder” provided by the world health organization (WHO). This principle is based on the serial introduction of drugs with increasing analgesic potency, titrated until pain relief is obtained. However, in patients with a severe and debilitating pain pattern, a more aggressive approach using opioids combined with adjuvant analgesics as first line therapy (i.e. a top-down approach), is useful to control pain and prevent sensitization of central pain pathways.”

3. References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

On behalf of all authors,

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