Manuscript Submission Cover Letter
To World journal of gastroenterology

Invitation for manuscript: number ID: 00058466 Special issue celebrating the 20th anniversary of WJG

Thursday, October 30, 14

Dear editor,

Herewith we would like to submit our revised version of the manuscript “Chronic pancreatitis as a model of visceral pain: A systematic mechanism-orientated approach” to world journal of gastroenterology.

Based on the reviewers’ comments, we have changed the title of the manuscript to: “A systematic mechanism-orientated approach to chronic pancreatitis pain”.

We thank the reviewers for their most useful and constructive comments. As a result, we have revised the paper extensively according to the comments of the editors and reviewers. Our detailed responses to the reviewers’ comments are to be found on the next pages. Our reply to the reviewers is in italic.

Our changes to the manuscript are extensive. Because of this no markings were used for changes in the revised manuscript.

We state that the present article has not been submitted or published elsewhere, that all the authors have participated in the writing of the article and agree with its content, and that there have been no sources of outside support for research or financial support from industry over the last five years concerning this study.

We hope that the manuscript is now suitable for publication.

With many thanks for your interest and best regards,

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Reviewer 1:

In their review "Chronic pancreatitis as a model of visceral pain: A systematic mechanism-orientated approach" Bouwense et al. aim to highlight the recent progress in understanding the central mechanisms underlying chronic pain in CP and its impact on pain management. The review is written in excellent english and the references are well chosen. However, due to several points, we can not recommend the MS for publication.

Major points:

1. The MS is too extensive. With more than 6000 words and 44 pages the authors should avoid redundancy and should avoid to give unnecessary information. - number of references should also be reduced. Many statements are substantiated by up to 6 references. Please only give the relevant references (max. 80).

The manuscript has been shortened by removing redundancy, tables and unnecessary information. The sections regarding IBS have been deleted, and the main focus of our manuscript is now only on abdominal visceral pain syndromes. The number of references has been reduced substantially from 134 to 89 references.

Minor points:

1. Page numbers are missing

Page numbers have been added

2. Typo in graph "peripheral sensitization": please delete "ENREF_26". This continues through the MS.

Both points have been adjusted in the manuscript

Reviewer 2:

In their current extensive review, Bouwense et al. provide a detailed description of the key concepts related to alterations in central pain processing in visceral pain syndromes with a particular focus on chronic pancreatitis (CP). They define four key questions in a mechanism-orientated approach that allows the idenfication of the source of peripheral nociception, and particularly the independence of central pain processing from the peripheral noxious stimulus. They also define the criteria for the development of any pain assessment tool that shall serve to decipher altered central pain processing. The authors have hereby provided a broad overview of their substantial past and current work that have helped to elucidate several novel aspects of visceral pain. The review is written in a didactic fashion, reminiscent of a book chapter. It is certainy going to be an important contribution to the field. However, I have two major and some minor comments related to this article:

Major comments:

1. The authors should aim at modifying this review to become a text that goes even more beyond a reiteration of the literature. This modification can be achieved if they applied the four key questions they posed in the Table 2 for formulating a concrete diagnostic algorithm for visceral pain. The article stems from a group with extensive expertise in this area. For exactly this reason, I would have rather expected a manuscript that makes a new proposal, i.e. a new conceptual advance. There is currently need for a novel diagnostic algorithm for visceral pain, and the group that wrote this review is the most likely group who can fulfill this need. Such an algorithm would also truly fulfill the premise that the reader extracts from the title of this article. Concretely, which of the described diagnostic tools, i.e. QST, EEG and fMRI should be applied in which patients in which order? Are there patients in which these tests are not applicable? Once such an algorithm is proposed for CP, can it also be extended to the study of chronic pain in other visceral disorders?

Thank you for the constructive suggestions. We have extensively rewritten the MS reflect the reviewers' comments. We have also added and discussed a management algorithm in the last paragraphs and figure 2. The algorithm can also be used for other chronic visceral pain syndromes as well.

Page 17, paragraph 3: the authors should discuss pancreatic resections (e.g. head resections) as a powerful tool of pain relief in selected cases of CP and cite clinical trials that deal with this issue.

We agree that surgery has shown good results in terms of pain relief on short and long term. In our manuscript we focus more on the central changes in pain processing and less on the conservative and/or surgical/endoscopic therapy of CP. However, in the introduction section more information is provided on invasive treatments for CP and included total pancreatectomy. As a reference a recent review has been added which summarizes al large trials on endoscopic and/or surgical treatment of CP.

Minor comments:

1. Abstract, page 4, line 66: please provide examples for some "other visceral pain syndromes".

The sentence has been deleted and now the first sentence of the abstract states:

"Pain in chronic pancreatitis (CP) shows similarities with other visceral pain syndromes (i.e. inflammatory bowel disease and esophagitis), which should thus be managed, in a similar fashion".

2. In the discussion of pain mechanisms in CP, considering citing 1) Barreto & Saccone. Pancreatology 2012, and 2) Demir et al., Langenbecks Arch Surg 2011.

Both references have been added to section regarding pain mechanisms in CP.

3. Page 14, line 322: A suitable tool for pain diagnostics should also document the function and changes in the peripheral nervous system.

More information and proof has been added to the sections: "Evidence for a systematic mechanism-orientated approach to chronic pain" and "Implementing a systematic mechanism-orientated approach to chronic pain in clinical practice"

Reviewer 3:

Minor comments:

1. In the abstract and later in the paper, the authors state that increased intrapancreatic pressure within the parenchyma and/or pancreatic duct causing tissue ischemia (due to pancreatic duct strictures and stones) is one of the common mechanisms causing pancreatic pain. I have no problem to see the connection regarding the stones and the following complications. But we also have the duct strictures, originating either from tissue ischemia or can it be inflammation? Is the increased intrapancreatic pressure secondary to the initial changes (inflammation?) in the pancreatic tissue? If so, then the authors should accentuate this. In addition, this may also influence Table one, especially the order of mechanisms.

In the introduction we have added more background information on the peripheral mechanisms causing pain together with their therapy. In the second paragraph of the section "Evidence for a systematic-mechanism orientated approach to chronic pain" we have also added more background information. The focus of our review was mainly on other sources (central nervous system) of chronic pain in CP, that is why we provided limited information on the already known peripheral sources of pain.

2. The authors state that they will focus on: QST, EEG and fMRI research concerning their application in chronic abdominal pain disorders such as chronic pancreatitis. In reality they focus on inflammatory visceral pain disorders i.e. CP and IBS representing a non-visceral i.e. altered visceral sensitivity phenomenon.

We agree with the reviewer that the origin of pain differs between CP and IBS. The sections regarding IBS have been deleted, and the main focus of our manuscript is now only on abdominal visceral pain syndromes with a known nociceptive focus.

3. Regarding the EEG in chronic visceral pain: Resting state EEG. The authors state that in IBS patients, power spectrum analysis of the resting EEG showed a decrease of alpha power percentage together with an increase of beta power percentage compared to healthy subjects. They also report an increase in amplitude strength in the theta and alpha band in patients with CP compared to healthy controls and a significant shift toward lower

frequencies in patients with CP compared with healthy controls. This was observed as a decrease in peak alpha frequency (PAF) over all scalp electrodes. I would suggest the authors to use a more united terminology or if not possible to try to clarify the different findings between the two states, if any. In my opinion this will shed light on the two different states. Furthermore, in the summary of this chapter the authors state that alpha activity in the resting state EEG has been shown to be affected in multiple chronic pain states. In other words they state that there is a change in the default state of the brain as a result of chronic pain. Do we really need an EEG to confirm that there is a change in the brain activity in pain disorders? In my opinion the authors should clarify how the future use of EEG (resting and evoked) could be used in a mechanism-orientated approach.

The analysis of resting state EEG in the context of chronic pain states is still in its infancy, and the associated terminology remains diverse. Whether we "need" EEG to prove changed brain activity in pain disorders is a moot point: we present the published research EEG data as further support for the presence of altered CNS processing and state in pain conditions. We have shortened and sharpened the section on EEG to reflect this. Furthermore we have made it clear that we do not consider EEG suitable for routine pain diagnostics at present.

4. In the conclusion the authors state that QST may be helpful in diagnosing all the four questions in Table 2. Do this mean that QST can be used as a clinical tool to measure changes in the CNS accompanying chronic pain? Can the described actual QST setup be incorporated in the daily clinic, outside highly

Thank you for the suggestion, we have added an algorithm in the last paragraphs and figure 2. The algorithm can also be used for other chronic visceral pain syndromes.