

We appreciate the reviewers comments. We agree this is a difficult subject and have attempted to bring more clarity to it. Our focus is on the use of pancreatic enzymes in the treatment of pain in chronic pancreatitis (i.e., pancreatic pain). We have tried to be comprehensive yet focused on pancreatic enzymes. The paper has a number of original conclusions in that it for the first time was able to reconcile the seemingly conflicting results of trials of enzymes in animals and in man. We start with defining pancreatic pain and point out that it has different origins and that it is often impossible to distinguish chronic pancreatic pain related to maldigestion and that coming from the pancreas. We discuss the potential mechanisms of generation of pain in chronic pancreatitis. Importantly, they are inter-related such that any one intervention can potentially effect many different pathways. We briefly discuss each of the potential mechanisms and their inter-relations before getting to the "meat" which is the section regarding **NEGATIVE FEEDBACK INHIBITION OF PANCREATIC SECRETION** which is the primary mechanism thought to be responsible for pancreatic enzymes effect. This section contains an original new synthesis of the available data in animals and humans. This is the longest section in the paper as it provides details of the physiology and the interactions involved. When one corrects for doses and formulations of the enzymes used and for the specificity of the enzyme inhibitors used to provoke enzyme secretion, the data becomes much more uniform and the seemingly contradictory studies become instead confirmatory. We believe that this section alone will be responsible for many subsequent citations as it provides clarity to what to this point has been a very confusing set of data.

We then go on to discuss the available clinical trials and meta-analyses is some details in that most of the studies were flawed in term of their analysis of pain and or the products used. Nonetheless, some were well done and deserve to be highlighted as they provide models for studies that are needed to better utilize enzymes for pancreatic pain and insufficiency. We conclude that section by saying " In conclusion, the heterogeneity in terms of patient characteristics (e.g., presence, absence and severity of exocrine insufficiency, etiology of pancreatitis, reason for presentation, use of narcotics, formulation, dosage, and

administration of enzymes in relation to meals, etc.) greatly affects the outcome of studies attempting to evaluate pain relief in chronic pancreatitis.

Heterogeneity makes meta-analysis a very blunt instrument for evaluation of the effectiveness of therapy or for helping to decide which therapy is ideal for an individual patient. Clearly some patients respond. Current enteric-coated enzyme products are unlikely to be highly effective either in terms of providing sufficient intraduodenal trypsin activity to engage the feedback mechanism or to fully correct steatorrhea. Protease activity is less sensitive to acid than is lipase, which is irreversibly inactivated at pH 4 or below. Future studies should either focus on trying to understand why those patients respond or to carefully select parameters thought to be important, such as providing a critical amount of trypsin or chymotrypsin activity into the duodenum. One can reasonably conclude that patients with exocrine pancreatic insufficiency benefit from correction of malabsorption and the ensuing nutritional deficiencies as well as improvement of gastrointestinal symptoms including pain associated with malabsorption. Reviews of the issues with providing adequate delivery of pancreatic enzymes for treatment of malabsorption are recommended for those wanting additional details regarding use of pancreatic enzymes for malabsorption.

Our concluding sections deal with use of pancreatic enzymes in general, a area where we have provided considerable original research, and the important issue of pain management especially in this era of increased recognition of opioid addiction. We also provide detailed recommendations regarding the data needed to manage often occult nutritional deficiencies present in these patients and often contributing to their disabilities.

Overall, we believe that the paper is comprehensive, concise for the number of issues covered, and very informative with new analyses and guidelines for current patient management.

## Response to the reviews

*Reviewed by 00947129*

Hobbs et al. review the management of pain in chronic pancreatitis with a focus on the role of exogenous enzyme administration.

Major points 1. The paper is well written, however, the authors seem to have no original data on this topic.

Response: We do not agree with this reviewer. As noted above no one has previously attempted to pull the data detailed data from physiologic studies of feedback inhibition of pancreatic enzyme secretion (the primary mechanism thought to be responsible for the effectiveness of pancreatic enzymes) together. We show that rather than being a collection of conflicting results, the majority of the results confirm and extend the validity of the notion and the physiology involved. This and other sections contains many new insights and syntheses that should form the basis for new experiments leading to improved patient care. In addition your analyses of the clinical data provide a road map for how to do the studies required to understand how to use enzymes and in which patients they should be expected to work. This is the purpose of a review.

2. Another weakness of the paper is that almost 60% of the cited papers have been published before 2000. The authors should concentrate on more recent data, some of which has not been discussed. I would also refrain from quoting (outdated) abstracts and foreign language publications.

Response: We have always believed that authors should be cited for what they contributed not when the paper was published. Our ability to look back and reanalyze the prior extremely well done physiology data allowed us to find reasons why results that seemed to provide conflicting results actually provided confirmations. These studies are detailed and complex studies of the physiology and will likely never be done again as they were definitive. We avoided quoting abstracts and foreign language publications unless they were critical (eg, some meta-analyzes focused a considerable portion of their article on abstracts that have never been published).

3. I think that a figure on the feedback inhibition of pancreatic secretion would strengthen the manuscript.

Response: We thought about this but the physiology is very complex which would require a figure that was also very complex and would never be referred to.

Minor points 1. Near the middle of page 3: ...the altered feedback mechanism?

2. Page 3, line 2 from the bottom: enzyme instead of enzyme. 3. Near the

middle of page 7: history is written three times in one sentence. 4. Page 9, line 1 of paragraph entitled Pathogenesis of pancreatic pain: "th" in 19th should be in superscript. 5. The paper is somewhat repetitious. E.g. the inactivation of lipase by low pH is mentioned on pages 26 and 27.

Response: We thank the reviewer for finding these mistakes and have corrected them.

*Reviewed by 00199523*

Corrections are made in track changes and uploaded. see pages 3,4 and 5. Article is too long, it should be shortened. (paper corrected)

Response: We thank the reviewer. It seems we had a run away spell check when we did our last review and did not notice the changes. We agree the paper is long but each section is actually very condensed even the sections where we provided actual data to explain feed back inhibition and examined the clinical trials in detail. The issue is that there are so many different mechanisms to take into consideration and even a brief discussion of each takes up space. The advantage of this journal is that authors can, within reason, explain complex ideas adequately.

*Reviewed by 03104779*

Points Minor: There are not the data from the authors' center to compare the merits of different treatment methods and put forward the preferred treatment options.

Response: First, this is a critical review, now original research. However, as noted above we have made original observations showing that the data that seemingly contradicted other data were most often confirmatory when corrections were made based on the differences in methods and test articles. As far as treatment, we agree that there is "no one size fits all" for this problem in relation to therapy. There is however, a preferred approach as outlined in Figure 1 that directs the physician to consider what factors need attention and an approach to when to implement different medical and surgical treatments. Our focus is on the rational for use of supplemental enzymes and data from our center have played a significant role in comparing enzyme formulations.

***Reviewed by 03552482***

I commend authors for the review of the article titled "Management of pain in chronic pancreatitis: Role of exogenous pancreatic enzymes." It is well thought out and well written. The references are appropriate, and the discussion of the results is balanced. It provides an excellent review of the theories of pain in chronic pancreatitis as well as overview of the treatment techniques for the pain associated with chronic pancreatitis. The authors then focus on the role of exogenous enzymes in pain relief. The discussion of the results is balanced as

the authors appropriately concluded that the results have been unclear due to insufficiently controlled experiments that have been reported. I would recommend the article be accepted as is with only corrections of very few minor grammatical errors.

Response: we agree.

Reviewed by 00034432

Authors

? The title is misleading because the authors reviewed the causes of pain in chronic pancreatitis and its management with various approaches and not only the role of exogenous pancreatic enzymes. ? Several meta-analyses and subsequently various guidelines report the non efficacy of pancreatic extracts in pancreatic pain. All the randomized studies shows the reduction of abdominal pain (not pancreatic pain) due to maldigestion in patients with severe exocrine pancreatic pain and chronic pancreatitis. ? No news or hypothesis are reported in the text that is useful for students but no fro practical gastroenterologists. ? Several papers have been missed and the authors should apply a better search strategy in medical databases

Comment: The title is misleading because the authors reviewed the causes of pain in chronic pancreatitis and its management with various approaches and not only the role of exogenous pancreatic enzymes.

Response: We no not agree as we focus on the role of exogenous enzymes which can play a role in many of the proposed pain mechanisms. We have revised the title as suggested to now be "**Management of pain in chronic pancreatitis with emphasis on exogenous pancreatic enzymes**" We agree with review #03552482 who said " It provides an excellent review of the theories of pain in chronic pancreatitis as well as overview of the treatment techniques for the pain associated with chronic pancreatitis. The authors then focus on the role of exogenous enzymes in pain relief. The discussion of the results is balanced as the authors appropriately concluded that the results have been unclear due to insufficiently controlled experiments that have been reported".

Comment: Several meta-analyses and subsequently various guidelines report the non efficacy of pancreatic extracts in pancreatic pain. All the randomized studies shows the reduction of abdominal pain (not pancreatic pain) due to maldigestion in patients with severe exocrine pancreatic pain and chronic pancreatitis.

Response: We devoted a large portion of the manuscript to discussion of the strengths and weakness of these papers. As noted above we believe we provide balance "discussion of the results is balanced as the authors appropriately concluded that the results have been unclear due to insufficiently controlled experiments that have been reported".

Comment: No news or hypothesis are reported in the text that is useful for students but no for practical gastroenterologists. ? Several papers have been missed and the authors should apply a better search strategy in medical databases

Response: The reviewer failed to provide even one example of an important paper on the use of pancreatic enzymes in pancreatic pain that was missed and how that might have changed our conclusions. We do not believe that we missed any critical studies from the sections of the papers related to the mechanisms, physiology, or use of pancreatic enzymes. We did summarize those sections that were needed to explain the problem such as the many studies on neurophysiology. That area alone would require a full paper and we point the reader to recent reviews to allow them to quickly access that literature. We also point out that despite the large amount of research the concept will not currently explain who relief of obstruction or enzyme therapy works.