May 29, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11296-review.doc).

**Title:** Visceral Hypersensitivity and Electromechanical Dysfunction as Therapeutic Targets in Pediatric Functional Dyspepsia

**Author:** John M Rosen, Jose T Cocjin, Jennifer V Schurman, Jennifer M Colombo, Craig A Friesen

**Name of Journal:** *World Journal of Gastrointestinal Pharmacology and Therapeutics*

**ESPS Manuscript NO:** 11296

We appreciate the feedback from reviewers that the manuscript is well-written and should be considered for publication. The manuscript has been improved according to the editor and reviewer suggestions as follows:

**Editor**

1. Core Tip section was added according to recommended structure and content.
2. References are now denoted in bracketed superscript.
3. References now include DOI and PMID when applicable.

**Reviewer 00037816**
**In this manuscript, authors reviewed the role of visceral hypersensitivity and electromechanical dysfunction in FD, and described the therapies for pediatric FD. The manuscript is well written and provides important clinical implications for physicians and gastroenterologist. Authors need to mention about COI in the manuscript, otherwise fine.**

1. We appreciate the feedback that the manuscript is well-written and pertinent to physicians and gastroenterologists.
2. COI information is included in the revised manuscript as recommended.

**Reviewer 00055108**
**In general this is a well written and extensive review regarding Visceral Hypersensitivity and Electromechanical Dysfunction as Therapeutic Targets in Pediatric Functional Dyspepsia**
**It could be somewhat more focused on the pediatric population when it comes to evaluation and possible therapy, but of course most of the studies on the functional dyspeptic patient have been studied on an adult population. One should also bear in mind the former studies executed in the eighties and nineties have metrological issues regarding gastrointestinal biomechanics potential affecting results.**

1. Thank you for your comments regarding the review. We agree that more focus on pediatric studies is ideal, but identified, as you did, that most studies in functional dyspeptics are in adults.

**Comments to Assessment of Visceral hypersensitivity;**

**You describe several possible investigations methods, mostly applied in an adult population, but you are not mentioning anything regarding a combined modality approach i.e. multimodal device which has been used the last decade in pain/biomechanical studies of the upper GI-tract. The multimodal investigation approach could shed some light on your discussion how to evaluation a FD-patient.**

1. The multimodal approach is an important concept in the evaluation of pain and biomechanics of the upper GI tract. Many of the studies included in this review performed several tests measuring somewhat different aspects of sensation or biomechanics. A comment emphasizing the importance of utilizing multiple tests (i.e. not relying on a single test) is added to "assessment of visceral hypersensitivity": In many studies, tests of visceral sensitivity are conducted in a multimodal design, both to determine correlation and to validate outcomes.

**Regarding the *Gastric Barostat* method as the gold standard could be questions these days, but of course several of the index studies regarding FD have been executed using Barostat.**

1. We agree that gastric barostat is a questionable gold standard, but is still often the standard to which many methods are compared due to its use in several index studies. This is an important distinction and the qualification "traditional" is added to the text regarding gastric barostat as a gold standard.

**Comments to assessment of Electromechanical dysfunction;**
**Consider to implicate possible information provided by the *Smart pill* on GI-function.**

1. Smart pill, or wireless motility capsule, is a newer modality that may provide additional information regarding electromechanical function. It may serve as a complementary study or perhaps supplant other methods of assessing gastric emptying or antroduodenal motility. The wireless motility capsule is mentioned in the original manuscript, but the revised manuscript adds a specific paragraph highlighting relevant Smart Pill literature: **Wireless Motility Capsule** The WMC shows promise as a relatively noninvasive, clinically relevant measure of gastrointestinal motility[115]. It is used to study prokinetic medication efficacy[116] and to describe an adult irritable bowel syndrome cohort[117]. Data is not yet available in adult or pediatric dyspeptics, but an initial study suggests the WMC is a sensitive detector of motor abnormalities in pediatric patients with upper gastrointestinal symptoms[118].

**Reviewer 02371383**

**The manuscript is well written and gives a good overview of the field. One figure and no tables are included. I suggest including tables on: 1) studies on visceral sensitivity in children 2) studies on electromechanical dysfunction in children and 3) different treatment alternatives.**

1. We appreciate the feedback that the manuscript provides a good overview and agree that addition of tables may be useful for the reader. Recommended tables 1 and 2 are included in the revised manuscript as a combined Table 1. Treatment alternatives studied in pediatric FD and related disorders are included in Table 2. We hope that the tables of studies added to the revised manuscript, in addition to the text itself, will provide enough direction to the reader.

**Reviewer 02442330**

**Please, include or comment: "visceral hypersensitivity" It should be mentioned that the visceral hypersensitivity could be caused either peripherally, centrally or both and may reflect allodynia, hyperalgesia and/or hypervigilance.**

1. We agree that pain sensation may be a result of many different pathways and that the definition can be parsed to improve accuracy. There is a sentence in the original manuscript under the heading "Visceral Hypersensitivity" that is now modified to include hyperalgesia and allodynia: "However, the subjective interpretation may change due to increased frequency or amplitude of the visceral stimulus, or increased sensitivity to a typically painful

(hyperalgesia) or nonpainful (allodynia) stimulus. Visceral hypersensitivity may result from alterations in the peripheral or central nervous system and has complex but increasingly understood etiology".

**"gastric accommodation" Tack et al have observed an association between early satiety and impaired gastric accommodation (Gastroenterology 1998; 115: 1346-52).**

1. Although the data on association between gastric accommodation and early satiety is mixed, it is an important point to include in the review. The original manuscript contains the following statement referencing Tack's 1998 Gastroenterology article (Ref 93) in the "Gastric Accommodation" section: Impaired accommodation has been associated with early satiety in some but not all studies[84, 91, 93]." We can expand if the reviewer feels more information is needed.

**"targeting visceral hypersensitivity" Peura et al (Lansoprazole in the treatment of functional dyspepsia: two double-blind, randomized, placebo-controlled trials. Am J Med 2004; 116: 740-8) have demonstrated that PPI are only effective in patients with acid predominant dyspepsia (? non erosive reflux disease should be excluded by 24h-pH/impedance measurement)**

1. Peura's study adds to the discussion of why PPI therapy may be effective in adults with FD, in that it may treat NERD which is a component of symptoms in some FD patients. A statement in the section "targeting visceral hypersensitivity" is added to reference the study and the important distinction it makes: "A randomized, controlled trial in adults found that PPI therapy improved symptoms only in FD patients with concurrent heartburn."

**Prucalopride: Bouras et al. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. Gastroenterology 2001; 120: 354-60.**

1. Prucalopride data including that by Bouras are very interesting in that Prucalopride has promotility effects, possible effects on visceral sensitivity, and is effective in treatment of constipation. It theoretically could be efficacious in FD, although we are not aware of any data supporting this hypothesis. Still, as the reviewer suggests it is important to mention that $5HT_4$ receptor agonists continue in development and clinical use, so the revised manuscript includes modified language in the "targeting electromechanical dysfunction" section and adds the Bouras reference: "Cisapride and newer 5-$HT_4$ receptor agonists regulate intestinal motility through effects on enteric cholinergic neurons, enhancing gastric emptying and accomodation, as well as potentially modulating visceral sensitivity."

**Domperidone data in adults (for other substances also reported): Halter et al, J Physiol Pharmacol 1997; 48: 185-92; Van Outryve et al, Scand J Gastroenterol Suppl 1993; 195: 47-52.**

1. Domperidone data in adults with FD is well-established and additional references are added including those recommended above as well as a meta-analysis (van Zanten 2001). The specific studies recommended provide interesting head-to-head comparison between domperidone and cisapride, and this is mentioned in the revised manuscript.

**Further pharmacologic data about therapy of impaired gastric accommodation: Ondansetrone; Marzio et al, Dig Liver Dis 2008; 40: 188-93 Sumatriptan; Malatesta et al, Dig Dis Sci 2002; 47: 2591-5 Tandospiron; Miwa et al, Am J Gastroenterol 2009; 104: 2779-87**

1. Data regarding ondansetron, sumatriptan, and tandospirone supports the idea that impaired gastric accommodation may be associated with symptoms in FD, and that treatment directed at gastric accommodation is effective in some patients. The referenced articles and statements below are added to the revised manuscript in "targeting electromechanical dysfunction":

a. Sumatriptan, also a 5HT1 receptor agonist, alters gastric size in dyspeptics, but specific mechanical effect and association with symptom improvement remain unclear.
b. A subset of FD patients also showed improvement in nausea and accommodation when treated with ondansetron, a $5HT_3$ antagonist, but mechanical and clinical effects were disassociated.
c. Tandospirone, a partial 5HT1a agonist similar to buspirone, also improved symptom scores in FD adults, but had no effect on early satiety implicating central anxiolytic effects rather than altered gastric accommodation.

Thank you again for considering publication of our manuscript in the *World Journal of Gastrointestinal Pharmacology and Therapeutics.*

Sincerely yours,

John M Rosen, MD

Division of Pediatric Gastroenterology, Hepatology, and Nutrition

Children's Mercy Kansas City

2401 Gillham Road

Kansas City, MO USA

E-mail: jmrosen@cmh.edu