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Authors' reply

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We would like to thank Kountouras *et al* for their comment on our review recently published in *Annals of Gastroenterology* [1]. Kountouras *et al* emphasized the potential effect of trimebutine in modulating symptoms related to both irritable bowel syndrome (IBS) and gastroesophageal reflux disease (GERD), especially when these symptoms overlap in the same patient.

As reported in the scientific literature, trimebutine seems to have a role in modulating hypermotility and hypomotility disorders, hastening gastric emptying, shortening the lag period, modulating visceral sensitivity and ameliorating gastrointestinal symptoms [2]. However, the use of trimebutine in clinical practice is not strongly supported by current evidence. In fact, some criticisms should be taken into account: a) only one study evaluated the potential effect of trimebutine in controlling gastrointestinal symptoms in patients with GERD-IBS overlap [2]; there are no data supporting the effects of trimebutine in hyper- or hypocontractile motility esophageal disorders; c) there are no data supporting the effects of trimebutine in GERD; and d) the effectiveness of trimebutine in treating IBS and overlapping functional dyspepsia (FD) is barely supported by literature.

Having said that, it is essential to underline the limited overlap between "true" GERD and IBS, as well as between GERD and FD [1,3]. A large number of studies aimed to detect these groups of patients; however, only few of those were performed according to pathophysiologic criteria [4,5]. As previously reported in pathophysiological studies [4-6], IBS appears to overlap more frequently with esophageal functional disorders rather than with GERD. Therefore, we can support the hypothesis that the effects of trimebutine in patients who complain of heartburn and have negative upper endoscopy (who may be hurriedly defined as GERD) are most likely due to its role in treating functional esophageal disorders, rather than controlling the GERD-related presentation. Indeed, recent functional investigations performed with the impedance-pH technique have provided significant evidence that endoscopy-negative patients with typical reflux symptoms are remarkably heterogeneous from a pathophysiological and histological standpoint and can be subdivided into true GERD and functional esophageal disorders [7-9].

Recently, pathophysiological studies have shown that functional esophageal disorders overlap more frequently with IBS or FD than with GERD [1,3,10]. In support of this contention, some studies have suggested that FD and IBS may share common pathophysiological mechanisms, such as visceral hypersensitivity; thus, drugs acting as visceral pain modulators (such as antidepressants) may exert beneficial effects on both disorders when tested in separate trials [3]. The recent Rome IV criteria will probably reduce this previously reported and expected overlap between GERD and IBS or FD. A deeper understanding of the pathophysiology of such disorders might lead towards new therapeutic options in functional gastrointestinal disorders.

References

1. de Bortoli N, Tolone S, Frazzoni M, et al. Gastroesophageal reflux disease, functional dyspepsia and irritable bowel syndrome: common overlapping gastrointestinal disorders. *Ann Gastroenterol* 2018;**31**:639-648.
2. Kountouras J, Chatzopoulos D, Zavos C, Boura P, Venizelos J, Kalis A. Efficacy of trimebutine therapy in patients with gastroesophageal reflux disease and irritable bowel syndrome. *Hepatogastroenterology* 2002;**49**:193-197.
3. de Bortoli N, Martinucci I, Bellini M, et al. Overlap of functional heartburn and gastroesophageal reflux disease with irritable bowel syndrome. *World J Gastroenterol* 2013;**19**:5787-5797.
4. de Bortoli N, Frazzoni L, Savarino EV, et al. Functional heartburn overlaps with irritable bowel syndrome more often than GERD. *Am J Gastroenterol* 2016;**111**:1711-1717.
5. Savarino E, Pohl D, Zentilin P, et al. Functional heartburn has more in common with functional dyspepsia than with non-erosive reflux disease. *Gut* 2009;**58**:1185-1191.
6. Savarino E, Zentilin P, Dulbecco P, Malesci A, Savarino V. The role of acid in functional dyspepsia. *Am J Gastroenterol* 2011;**106**:1168.
7. Savarino E, Marabotto E, Zentilin P, et al. The added value of impedance-pH monitoring to Rome III criteria in distinguishing functional heartburn from non-erosive reflux disease. *Dig Liver Dis* 2011; **43**:542-547.
8. Savarino E, Tutuian R, Zentilin P, et al. Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. *Am J Gastroenterol* 2010;**105**:1053-1061.
9. Savarino E, Zentilin P, Tutuian R, et al. Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. *J Gastroenterol* 2012;**47**:159-168.
10. Savarino V, Savarino E. Is acid relevant in the genesis of dyspeptic symptoms associated with nonerosive reflux disease? *Eur J Gastroenterol Hepatol* 2008;**20**:252-254.

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Conflict of Interest: None

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