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INVITED EDITORIAL

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Editorial: on the road towards treatment of gastroparesis—accelerating but do we get closer?

Gastroparesis represents an opportunity for new drug development considering its burden to the healthcare system and the limited currently available effective treatments. Gastroparesis prevalence has been estimated from 0.1 to 0.3% of the general population and keeps increasing as the incidence of diabetes grows.[1] Furthermore, gastroparesis is associated with high direct and indirect costs, decreased quality of life, and increased morbidity and mortality.[1,2] Effective therapy that successfully relieves symptoms would, therefore, be expected to be cost-effective. Moreover, reasonable side effects of any effective treatment may be acceptable as long as this treatment is associated with improved quality of life and reduction of associated morbidity/mortality. Since the diagnosis of gastroparesis is based on delayed gastric emptying, most drugs tested are prokinetic agents aimed to accelerate emptying with the hope of improving symptoms.

However, an unmet clinical need remains for pharmacological management of gastroparesis. Disappointingly, symptom improvement (when observed) has not always been related to gastric emptying acceleration.[3,4] In fact, despite significant acceleration of gastric emptying, some pharmacological interventions were not associated with clinical efficacy.[5] Also, serious adverse events including QT interval prolongation with domperidone and erythromycin, and extrapyramidal syndrome with metoclopramide, have led regulatory agencies to restrict their use. As a result, metoclopramide is currently the only treatment labelled for gastroparesis and, in the United States, is only approved for short-term use. Conversely, domperidone, erythromycin and prucalopride are used off-label in Europe and the United States for gastroparesis.

Among the different pharmacological classes of prokinetic agents, 5-HT_4 agonists followed a parallel road. For instance, revexepride failed to demonstrate significant acceleration of gastric emptying.[6] Mosapride accelerated gastric emptying but failed to demonstrate clinical efficacy on symptoms of gastroparesis.[7] Tegaserod and cisapride were removed from the market due to cardiovascular concerns although tegaserod has since been re-introduced in the United States, albeit not for gastroparesis. Prucalopride accelerated gastric emptying and improved symptoms but these effects were not clearly correlated.[3]

Velusetrag is a next-generation selective 5-HT_4 agonist with a favourable safety profile lacking cardiovascular side effects. Velusetrag accelerated colonic transit and gastric emptying in healthy volunteers.[8] In addition, velusetrag improved symptoms in patients with chronic idiopathic constipation.[9] In the study conducted by Kuo *et al*,[10] prokinetic effects of velusetrag were confirmed in patients with diabetic or idiopathic gastroparesis. In these patients, velusetrag was well tolerated and accelerated gastric emptying as demonstrated by a reduction of the gastric emptying half time measured using octanoic acid breath test. This study therefore provides promising data in the hope of validating a new treatment for gastroparesis. However, this phase IIa study was not designed or powered to assess symptomatic benefit in patients with gastroparesis.

Although multiple obstacles have been overcome by velusetrag in this difficult road towards gastroparesis treatment, demonstration of symptomatic efficacy in patients with gastroparesis remains the final, but probably the most difficult, step. Whether gastric emptying acceleration will translate into clinical efficacy is enthusiastically expected, but not guaranteed.

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LINKED CONTENT

This article is linked to Kuo et al papers. To view these articles, visit https://doi.org/10.1111/apt.16344 and https://doi.org/10.1111/apt.16395

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