Shedding new light on the causes and treatment of chronic unexplained stomach symptoms

Across the world, about one in six people suffer from chronic stomach symptoms, including feeling very full and uncomfortable or bloated after eating, being unable to finish a normal sized meal and experiencing after meals frequent stomach pains. These symptoms are called dyspepsia, literally meaning “bad digestion”. The symptoms often affect work, relationships and sleep, and frequently are accompanied by anxiety and depression. Routine tests including looking into the stomach and upper small intestine (duodenum) with an endoscope does not identify a cause in most cases, and the condition is then termed “*functional dyspepsia”* or FD (functional referring to a disorder of gut function leading to symptoms of “bad digestion”).

The gut has a very complex nervous system equal in complexity to the spinal cord, called the second brain, which helps ensure food moves comfortably and unobtrusively through the many feet of gut and can be absorbed. If the gut does not work, we do not survive. The stomach empties abnormally or fails to properly relax after a meal or is sensitive to stretch in many patients with FD. Until recently the underlying causes of FD however have been mysterious, but new research is revolutionizing the field.

A stomach bacteria that causes stomach and duodenal ulcers (*Helicobacter pylori*) also causes chronic indigestion in a few cases who are cured by antibiotic therapy. Other cases develop stomach symptoms after an acute bacterial gastroenteritis implicating intestinal inflammation in the disease. Recently, subtle inflammation in the duodenum (in particular, increased eosinophils) has been seen in FD, and the gut is leaky with activation of the immune system. It is possible the immune activation may signal the brain and trigger symptoms such as anxiety. Further, the bacteria in the duodenum appear to differ in FD from health, and may play a role in immune activation and disease development, an active area of exciting research.

Treatment of FD is currently limited, and no treatment is as yet curative. Drugs that work on the brain can work on the gut too. In clinical practice, an antidepressant seems to help some people with FD, but it has been unknown if antidepressants are better than an inert pill (placebo), or which types of antidepressants work, and if they work whether it’s in the brain or locally in the gut. Antidepressants acts via effects on neurotransmitters but this occurs throughout the body and not just in the brain.

In a large clinical trial conducted in the US and Canada, 292 patients with FD received an antidepressant (either amitriptyline 50mg, or escitalopram 10mg daily), or an inert pill (placebo). Only the amitriptyline was better than placebo in FD, and it particularly helped stomach pain. The next question was, does the drug work by reducing anxiety or improving sleep (i.e. does the drug work in the brain) or does it work by another mechanism?

We found the antidepressants did not improve psychological scores at 3 months on treatment compared with placebo. But amitriptyline did modestly improve sleep. It is unknown if this is the major mechanism leading to benefit or not. The antidepressants also alter neurotransmitter release in the intestines. In additional work, antidepressants were observed to relax the top part of the stomach which may be another reason they improve stomach symptoms. We found antidepressants do not improve stomach emptying.

There is now new hope for patients with chronic unexplained stomach symptoms. Fresh treatment options are emerging. More research is needed but we are beginning to better understand the underlying disease pathways, and as we learn more cure may be possible for many.

Nicholas J. Talley
Faculty of Health and Medicine, University of Newcastle, Callaghan, New South Wales, Australia

Publications

Effects of Amitriptyline and Escitalopram on Sleep and Mood in Patients With Functional Dyspepsia.
Herrick LM, Camilleri M, Schleck CD, Zinsmeister AR, Saito YA, Talley NJ
Clin Gastroenterol Hepatol. 2018 Mar

Effects of Antidepressants on Gastric Function in Patients with Functional Dyspepsia.
Lacy BE, Saito YA, Camilleri M, Bouras E, DiBaise JK, Herrick LM, Szarka LA, Tilkes K, Zinsmeister AR, Talley NJ
Am J Gastroenterol. 2018 Feb

Effect of Amitriptyline and Escitalopram on Functional Dyspepsia: A Multicenter, Randomized Controlled Study.
Talley NJ, Locke GR, Saito YA, Almazar AE, Bouras EP, Howden CW, Lacy BE, DiBaise JK, Prather CM, Abraham BP, El-Serag HB, Moayyedi P, Herrick LM, Szarka LA, Camilleri M, Hamilton FA, Schleck CD, Tilkes KE, Zinsmeister AR
Gastroenterology. 2015 Aug