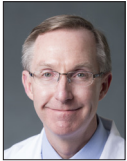


# ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

## Effects of Opioids on Esophageal Dysfunction



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**G&H** How prevalent is opioid use in the general population, as well as in people with esophageal diseases?

**BL** Opioids are increasingly being used to treat chronic pain, both cancer- and noncancer-related. The most recent year for which complete data on opioid prescriptions are available is 2012. In that year, 259 million prescriptions for opioids were written in the United States. Currently, approximately 3% of the US adult population is receiving long-term opioid therapy for noncancer pain. Interestingly, twice as many opioid prescriptions per person are written in the United States compared to Canada. Within the United States, significant variations in opioid prescribing patterns exist, with 3 times more prescriptions written in Alabama (the highest opioid-prescribing state) than in Hawaii (the lowest opioid-prescribing state).

Regarding opioid use in specific gastrointestinal (GI) populations, data are somewhat limited. The most useful data available are for patients with symptoms of constipation due to opioids, otherwise known as opioid-induced constipation. It is estimated that up to 41% of patients treated with opioids have symptoms of constipation. However, data are lacking from large prospective studies evaluating the incidence or prevalence of opioid-induced effects on the esophagus, including in patients with gastroesophageal reflux disease (GERD) or Barrett esophagus.

**G&H** What defines a chronic opioid user?

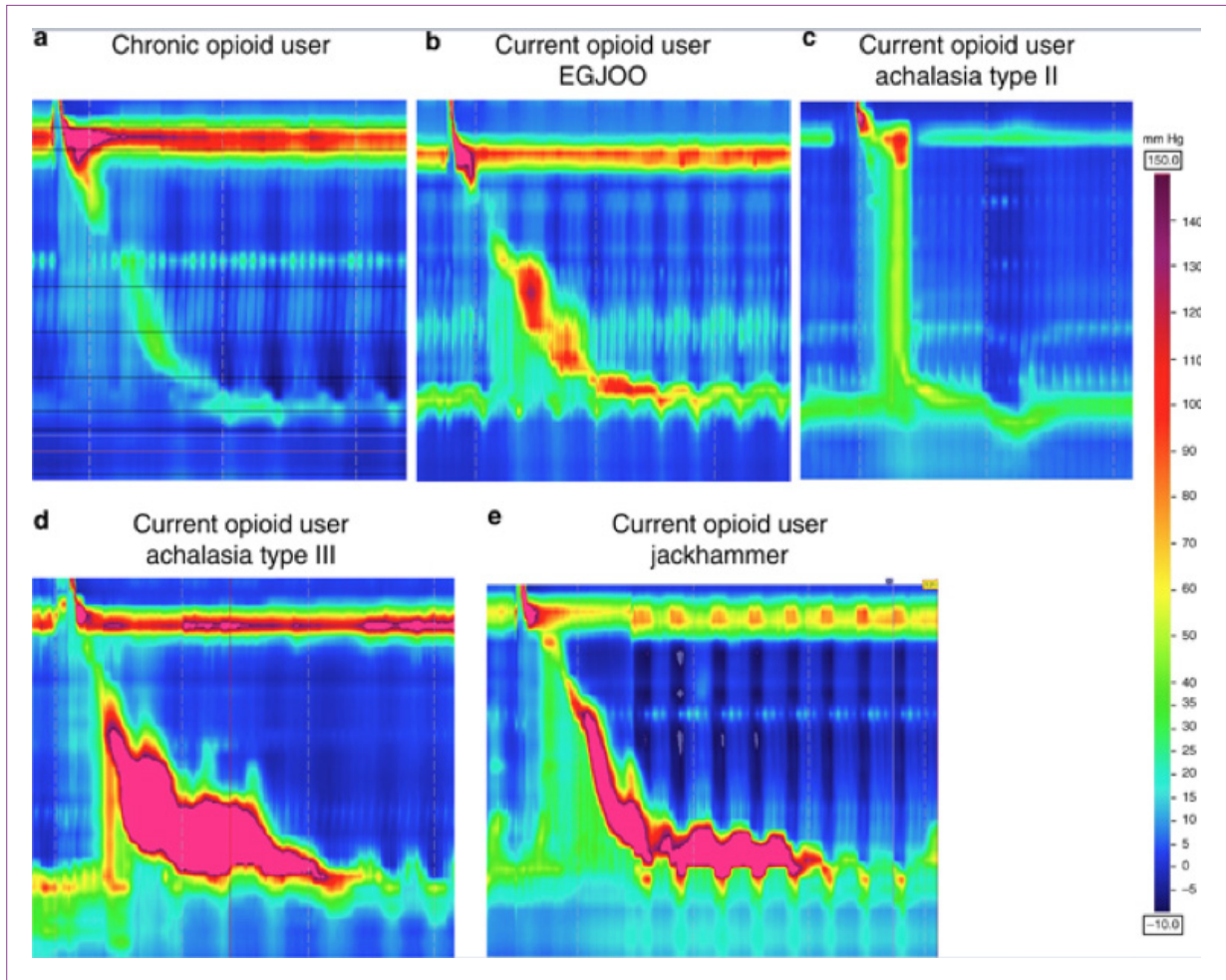
**BL** Although clinicians frequently define this patient differently, the majority of research studies and health care

providers who focus on pain management define chronic opioid use as daily use for at least 90 days.

**G&H** What are the main adverse effects associated with opioid use in regard to the GI tract and esophagus?

**BL** Adverse effects of opioids on the GI tract can be broadly classified into opioid-induced bowel dysfunction (OIBD) and narcotic bowel syndrome. OIBD, the more common of the 2 disorders, represents a broad spectrum of disorder motility that can involve the esophagus, stomach, small bowel, or colon and develops as a direct result of opioids on the GI tract. In contrast, narcotic bowel syndrome is characterized by a progressive and paradoxical increase in the severity of chronic abdominal pain despite the use of continuous or increasing doses of opioids prescribed to relieve such pain.

The pathophysiology of OIBD, which includes the effects on the esophagus, represents a peripheral effect mediated by the direct actions of opioids on opioid receptors (ie, mu, kappa, and delta) on enteric neurons within the GI tract. When opioid receptors in the GI tract are activated, either by exogenous or endogenous opioids, propulsive activity decreases; nonpropulsive contractions increase; normal activity of the migrating motor complex is disrupted; pancreatic, biliary, and gastric secretions decrease; and anal tone increases. These physiologic changes may lead to abnormalities in GI motility throughout the GI tract. In the esophagus, opioids can decrease esophageal peristalsis and change lower esophageal sphincter function. This may result in new or worsening symptoms of dysphagia and GERD.



**Figure.** Esophageal pressure topographies of a chronic opioid patient studied off opioids for at least 24 hours (A) and chronic opioid patients studied on opioids (B-E).

EGJOO, esophagogastric junction outflow obstruction.

Reproduced from Ratuapli SK, Crowell MD, DiBaise JK, et al. Opioid-induced esophageal dysfunction (OIED) in patients on chronic opioids. *Am J Gastroenterol.* 2015;110(7):979-984.

### G&H How does the use of opioids affect treatment of GERD and Barrett esophagus?

**BL** Data are lacking on the effect that opioids have on the treatment of GERD and Barrett esophagus. Physiologically, opioids impair normal esophageal peristalsis and slow gastric emptying. This combination of events increases the likelihood of reflux of gastric contents into the esophagus, which means that some patients who had managed symptoms of GERD with diet and lifestyle modifications may now require intermittent or daily medications to relieve symptoms. Similarly, patients who previously controlled GERD symptoms with a once-daily proton pump inhibitor may now require a higher or twice-daily dose.

The link between Barrett esophagus and chronic opioid use is likely, although research supporting the

association is limited. It stands to reason that a chronic opioid user might be more likely to have reflux and, thus, be at risk for Barrett esophagus. However, recently published guidelines on Barrett esophagus state that chronic opioid use is not considered a classic risk factor (in contrast to obesity, a hiatal hernia, sex, and age). These unanswered questions highlight the need for further research in this area.

### G&H Do certain opioids present a bigger risk in caring for patients with esophageal dysmotility?

**BL** There are multiple opioids available for clinical use for chronic pain syndromes. Some of the most common include hydrocodone, oxycodone, morphine, dilaudid,

and methadone. These agents differ in terms of efficacy and safety. Pain relief can be compared between different opioids using morphine equivalents; however, no study has prospectively evaluated the effects of different opioids, or different doses of opioids, on esophageal function. This would provide an ideal opportunity to look at different opioids and their effects on esophageal function and to perform dose-ranging studies.

**G&H** What is the recommended minimal amount of time that patients on opioids should stop medication prior to high-resolution manometry or other procedures?

**BL** Most opioids have a reasonably short half-life. A good clinical rule is that after 5 half-lives, the medication is nearly completely out of the blood stream. For instance, the half-life of hydrocodone is 6 hours. Thus, after 5 half-lives, or 30 hours, nearly all of the medication is out of the patient's body. In clinical practice, that means that stopping an opioid 1 to 2 days in advance of esophageal testing is appropriate. However, in the real-world setting, stopping opioids can be difficult for many patients, if not impossible.

**G&H** Can you describe the design of your study evaluating esophageal dysfunction and opioid use?

**BL** This study was brought about, in part, because Drs Shiva Ratuapli and Michael Crowell, along with the other authors of the study, recognized that opioids can cause esophageal dysfunction. The several small studies that have been previously published conflicted in information and used older, solid-state manometry catheters. We believed that a larger study using high-resolution esophageal manometry might shed some light on the association between opioid use and esophageal dysfunction.

Our retrospective study included 121 patients with symptoms of dysphagia (55%), GERD (26%), or chest pain (12%) who were identified as chronic opioid users. These patients were then divided into those who were taking opioids (55%) or those who had been off opioids (45%) for at least 24 hours (Figure). Both groups were very similar in terms of age, sex, and body mass. Patients were measured with a high-resolution esophageal manometry catheter and categorized using the Chicago Classification (version 3.0).

**G&H** What were the key findings of your study?

**BL** The key findings were that patients who were on opioids had a higher integrated relaxation pressure and were more likely to have type III achalasia and esophagogastric junction outflow obstruction than patients who had stopped opioid use. We found that opioids do not just cause constipation and slow stomach emptying, but can affect the esophagus.

Clinically, this means that if a patient on opioids presents with symptoms of dysphagia, and a high-resolution esophageal manometry finds esophagogastric junction outflow obstruction or type III achalasia, the clinician should consider whether the finding is inherent or if it is a side effect of opioid use. It is imperative to treat the patient with the appropriate therapy, and understanding the relationship between opioid use and esophageal dysfunction could prevent the patient from receiving medication he or she may not need.

**G&H** What are the next steps in research?

**BL** Unfortunately, opioid use in the United States continues to grow. This means that all health care providers will see more and more patients with symptoms of esophageal dysfunction related to opioids. Future research is needed to help us better understand which opioids are most likely to cause esophageal dysfunction and to determine whether there is a dose-related effect. I think we need to understand how quickly esophageal dysfunction occurs. Additionally, we need long-term studies to help us better understand the possible relationship between opioids and Barrett esophagus. Clearly, there are opportunities for research for investigators.

*Dr Lacy has no relevant conflicts of interest to disclose.*

**Suggested Reading**

- Agostini S, Eutamene H, Cartier C, et al. Evidence of central and peripheral sensitization in a rat model of narcotic bowel-like syndrome. *Gastroenterology*. 2010;139(2):553-563.
- Grunkemeier DMS, Cassara JE, Dalton CB, Drossman DA. The narcotic bowel syndrome: clinical features, pathophysiology, and management. *Clin Gastroenterol Hepatol*. 2007;5(10):1126-1139; quiz 1121-1122.
- Hutchinson MR, Bland ST, Johnson KW, Rice KC, Maier SF, Watkins LR. Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. *ScientificWorldJournal*. 2007;7:98-111.
- Ratuapli SK, Crowell MD, DiBaise JK, et al. Opioid-induced esophageal dysfunction (OIED) in patients on chronic opioids. *Am J Gastroenterol*. 2015;110(7):979-984.
- Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG clinical guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol*. 2016;111(1):30-50.