Q&A

CME Outfitters

Based on a CME Outfitters Live & On Demand webcast held on June 25, 2015

Faculty Response to Questions from the Live Webcast

Insights Into the Assessment, Prevention, and Management of Opioid-Induced Constipation

Q: What was the dose of lubiprostone in the Phase III studies that was shown to be most effective?

A: *In the dosing study, the dose that was most effective without an increase in adverse effects was 48 mcg/day (24 mcg/twice a day). This dose was chosen for subsequent Phase 3 studies. There was an increase in adverse effects at 72 mcg/day without a significant change in efficacy.1*

The approved dosage for lubiprostone for chronic idiopathic constipation and opioid-induced constipation is:[2] 24 mcg taken twice daily orally with food and water; Reduce the dosage in patients with moderate and severe hepatic impairment.

The approved dosage for lubiprostone for irritable bowel syndrome with constipation is:[2] 8 mcg taken twice daily orally with food and water; Reduce the dosage in patients with severe hepatic impairmen.

Q: Is there data to show that lubiprostone is safe for chronic use?

A: *In an open-label study, 248 patients took lubiprostone, 24 mcg twice daily, as needed for 48 weeks. Of the 248 patients who entered the trial, 127 (51%) completed the trial. A dose reduction was observed in 17% of the patients, resulting in an average study medication exposure across the study of approximately 1.7 capsules (or approximately 40.8 mcg) per day. The most common treatment-related AEs were nausea (19.8%), diarrhea (9.7%), abdominal distension (6.9%), headache (6.9%), and abdominal pain (5.2%). No deaths were reported and of the 16 reported serious AEs, one was considered possibly treatment related. Average changes in serum electrolytes were not clinically relevant at any time point during the study. On average, lubiprostone significantly ($p < .0001$) reduced patient-reported constipation severity, abdominal bloating, and abdominal discomfort across 48 weeks when compared to baseline. During this 48-week open-label study, lubiprostone was well tolerated. Bowel symptoms consistently improved over 48 weeks in adult patients with chronic idiopathic constipation.[3]*

Q: Can you talk more about how opioid-induced constipation happens, specifically, how is OIC tied to decrease in fluid in the colon?

A: *Stimulation of gastrointestinal mu-opioid receptors by opioids disrupts normal gut motility. This leads to non-propulsive contraction of the bowel wall, delaying transit time of intestinal contents. Also, reduced longitudinal muscle propulsive contractions increases trend to harder, drier stools. Also, opioids may reduce defecation reflex by decreased sensitivity to distention and increasing internal anal sphincter tone.[4,5]*

Q: Can you elaborate more about slow transit constipation? Definition, diagnosis, and treatment.

A: *Slow Transit Constipation (STC): delay of stool transit through the colon, due to a myopathy, neuropathy or secondary to an evacuation disorder such as dyssynergic defecation (difficulty expelling stool from the anorectum). In older individuals there are neurodegenerative changes in the enteric nervous system. Some studies have suggested a 37% loss of enteric neurons in those older than 65 compared to young adults. Also, studies have suggested age-related loss of neurons expressing choline acetyltransferase while sparing neuronal nitric oxide in the colon. This may lead to an increase in inhibitory neurons in the aging colon, with negative consequences on gut motility.[6,7]*

Q: Do over-the-counter NSAIDs and other agents also affect gut motility?

A: *It remains unclear whether NSAIDS have effects on gut motility. Several articles have reported an association between NSAIDS and constipation although whether NSAIDs or another confounding condition explains this association remains unclear.[8]*

Q: Do lubiprostone and naloxegol reduce the bloating associated with constipation?

A: *A study evaluating lubiprostone found that subjects randomized to 24 mcg BID reported reduced constipation severity, abdominal bloating, and abdominal discomfort compared to baseline.[9] In another study on lubiprostone for OIC reported a significantly higher response rate of SBM (27.1 vs. 18.9%) vs. placebo. Numerical differences were noted between treatment groups for abdominal bloating and abdominal discomfort, but those results did not reach statistical significance.[10] An additional study on lubiprostone in OIC did demonstrate improvements in abdominal discomfort, straining, constipation severity by patient diaries, but did not show improvement in abdominal bloating per patient diaries.[11] A recent randomized controlled study of naloxegol for the treatment of OIC did not measure abdominal bloating as a secondary end-point. Further studies are needed.[12]*

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Q: Can you talk more about the link between OIC and adherence to treatment? Patients are often so unhappy due to the constipation that they stop their pain medication and ask for different pain medication.

A: *Many times patients may report a previous "allergic reaction" to an opioid when it is merely related to a common adverse effect like constipation. More aggressive treatment for constipation early on, even prophylactically, may help improve chances of a successful trial of an opioid for pain.*[13]

In 2009, the American Academy of Pain Medicine recommended primary prophylaxis for OIC utilizing fluid, fiber, stool softeners, and laxatives for patients with chronic non-cancer pain syndromes. The findings of the 2012 American Society of Interventional Pain Physicians echoed these sentiments.[14]

Q: Is there a recommendation for getting chronic pain patients moving to address both constipation and also reduction in muscle tone? This is a big struggle with my patients.

A: *Clinicians should encourage patients with OIC to increase physical movement, including walking during the day. This will help to stimulate bowel motility. It is also imperative that clinicians talk with their patients about OIC at every visit and spend time asking their patients about not only constipation but hard stools and inability to completely evacuate. We need to ensure patients are comfortable discussing this topic with their healthcare providers and are aware that treatment options for OIC are available.*[15,16]

References

1. Johanson JF, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. *Aliment Pharmacol Ther*. 2007;25(11):1351-61. PMID: 17509103.
2. Highlights of prescribing information for Amitiza™ (lubiprostone) formulation. Drugs@FDA.gov. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021908s011lbl.pdf. Published April, 2013. Accessed August 5, 2015.
3. Lembo AJ, Johanson JF, Parkman HP, et al. Long-term safety and effectiveness of lubiprostone, a chloride channel (ClC-2) activator, in patients with chronic idiopathic constipation. *Dig Dis Sci*. 2011;56(9):2639-45. PMID:21769655.
4. Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *Am J Gastroenterol*. 2011;106(5):835-42. PMID: 21343919.
5. Leppert W. The role of opioid receptor antagonists in the treatment of opioid-induced constipation: a review. *Adv Ther*. 2010;27(10):714-30. PMID: 20799006.
6. Rao SS. Constipation: evaluation and treatment of colonic and anorectal motility disorders. *Gastroenterol Clin North Am*. 2007;36(3):687-711, x. Review. PMID: 17950444.
7. Bouras EP, Tangalos EG. Chronic constipation in the elderly. *Gastroenterol Clin North Am*. 2009;38(3):463-80. Review. PMID: 19699408.
8. Chang JY, Locke GR, Schleck CD, Zinsmeister AR, Talley NJ. Risk factors for chronicconstipation and a possible role of analgesics. *Neurogastroenterol Motil*. 2007;19(11):905. PMID: 17988275.
9. Lembo AJ, Johanson JF, Parkman HP, et al . Long-term safety and effectiveness of lubiprostone, a chloride channel (ClC-2) activator, in patients with chronic idiopathic constipation. *Dig Dis Sci.* 2011;56(9):2639-45. PMID:21769655.
10. Jamal MM, Adams AB, Jansen JP, Webster LR. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. *Am J Gastroenterol*. 2015;110(5):725-32. PMID: 25916220.
11. Cryer B, Katz S, Vallejo R, Popescu A, Ueno R. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. *Pain Med.* 2014;15(11):1825-34. PMID: 24716835.
12. Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med. 2014;370(25):2387-96. PMID: 24896818.
13. Chou R, Fanciullo GJ, Fine PG, et al. American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-30. PMID: 19187889.
14. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. *Pain Physician*. 2012;15(3 Suppl):S67-116. PMID: 22786449.
15. Kim YS, Song BK, Oh JS, Woo SS. Aerobic exercise improves gastrointestinal motility in psychiatric inpatients. *World J Gastroenterol*. 2014;20(30):10577-84. PMID: 25132778.
16. Liu LW. Chronic constipation: current treatment options. *Can J Gastroenterol*. 2011;25. Suppl B:22B-28B. Review. PMID: 22114754.

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