JAMA Insights | CLINICAL UPDATE

Update on the Management of Constipation

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Chronic constipation is very common. The most recent estimate of clinician visits attributable to constipation were from 2001 to 2004 and reported more than 8 million clinician visits in the United States, with most occurring in adult primary care settings (33%) followed by pediatric (21%) and gastroenterologist (14%) offices.[1] These encounters result in large expenditures for nonprescription laxatives and other bowel movement aids, such as enemas and suppositories.

Constipation may be associated with a primary or secondary motor disorder of the colon, a defecation disorder, a large number of diseases, or adverse events of drugs.[2] A time-honored approach to managing constipation is to exclude an organic cause with appropriate testing and to consider slow colon transit and defecation disorders only when standard treatments with available agents fail.[3] The diagnostic evaluation of constipation has not changed significantly since the publication of the American Gastroenterological Association guidelines in 2013.[3]

Related article

Since publication of a review on constipation in the January 12, 2016, issue of *JAMA*,[2] new information has emerged on the following important topics: (1) newer agents are now available in the United States for the management of chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C), (2) new peripherally acting μ-opioid receptor antagonists (PAMORAs) were approved for the management of opioid-induced constipation (OIC), and (3) new guidelines were published for the use of laxation agents and PAMORAs for the management of OIC. Additionally, squatting to facilitate defecation and squat assist devices have been recently commercially publicized.

Newly Available Pharmacologic Agents for CIC and IBS-C

Two intestinal secretagogues, linaclotide and plecanatide, target guanylate cyclase-C receptors on the intestinal epithelium to increase intestinal chloride and bicarbonate secretion into the gut lumen to enhance gastrointestinal transit.[4] Linaclotide was first approved for IBS-C (290 ug daily) and CIC (145 ug daily) in 2012. The US Food and Drug Administration (FDA) approved a 72-ug daily dose for the management of CIC. Plecanatide was approved for CIC (3 mg daily) that same year and for IBS-C (3 mg or 6 mg daily) in January 2018. A meta-analysis of 8 linaclotide trials (5 examining CIC and 3 examining IBS-C) and 7 plecanatide trials (4 examining CIC and 3 examining IBS-C) encompassing over 10 000 patients[4] concluded that there were no significant differences between the drugs concerning efficacy or adverse events, such as diarrhea (or diarrhea-related study withdrawals). Somewhat similar findings were reported in a network meta-analysis of individuals with IBS-C.[5] Given these observations, it is reasonable to conclude that either agent may be prescribed for both indications with similar anticipated results.

Another drug with a different mechanism of action was approved by the FDA for the management of CIC in December 2018. Prucalopride is a serotonin 4 receptor agonist that increases intracellular cyclic adenosine monophosphate to enhance release of acetylcholine, a major excitatory neurotransmitter in the gastrointestinal tract.[6] Because of potential adverse events associated with the low selectivity of previously released serotonin agonists (cisapride, tegaserod), which led to their withdrawal from the US market, there have been efforts to develop highly selective serotonin 4 agonists with low affinity for certain cardiac channels and enhanced cardiovascular safety. Prucalopride was released in Europe in 2010 and Canada in 2011 for the management of CIC. However, it was not until 2018 that the FDA approved its use for managing CIC based on 3 pivotal trials conducted in 2008 and 2009. This decision was largely due to the long postmarketing experience in other countries to reassure those with lingering concerns about cardiovascular safety. The usual recommended dose is 2 mg daily in individuals 65 years or younger and 1 mg daily in individuals older than 65 years. These recommendations are predicated on the slower elimination of the drug in older individuals, which is exclusively through renal excretion. It has an excellent safety record and is well tolerated.

Intestinal secretagogues and prucalopride should be used only if standard laxatives fail. They are more costly compared with standard laxatives and there is no evidence that they are more effective than currently available laxatives, such as bisacodyl, senna, or polyethylene glycol–based products (**Table**). In a review published in *JAMA* in 2016 on this topic,[2] a single-center study was cited that found polyethylene glycol 3350 to be noninferior to prucalopride in treating patients with CIC. The absence of comparator studies remains a shortcoming of our current system for determining cost-benefit analysis of laxatives. Prucalopride has not been approved for the management of IBS-C because of a lack of clinical trials examining the efficacy of this agent for IBS-C.

The Use of Squatting Posture to Improve Defecation

Recent studies have reported on the possible influence of body posture to enhance defecation and avoid constipation. Squatting to defecate is widely practiced in Asia and Africa, whereas sitting is the prevalent custom in the United States and other Western countries. Studies have shown that squatting straightens the anorectal angle to reduce straining to defecate.[7] Devices to promote a squatting or semi-squatting position have been commercially developed and, in their simplest form, involve a footrest that can be attached to a conventional toilet seat.

In the elderly population, with their increased prevalence of medical conditions, constipated individuals may have difficulty in flexing their hips or raising or lowering from a standing position to a squatting or semi-squatting position. The development of squat assist devices would be a major advance for any constipated adults with musculoskeletal disorders, particularly older adults.[7] At present, there is only anecdotal evidence to support the use of squatting devices, but they can be tried with little or no risk to individuals with constipation.

Table. Approximate Costs of Available Agents for Managing Constipation and Opioid-Induced Constipation (OIC)

Agents	Wholesale Cost per Month, US $[b]
Bulk agents	
Psyllium (10 g daily)	8.00
Nonabsorbed substances	
Polyethylene glycol 3350 (17 g daily)	9.00
Packet (17 g)	31.00
Lactulose (20 g daily)	13.00
Stimulants	
Senna (17 mg daily)	7.00
Bisacodyl (10 mg daily)	5.00
Secretory drugs[a]	
Lubiprostone (8-24 µg twice daily)	445.00
Linaclotide (72-290 µg daily)	509.00
Plecanatide (3-6 mg daily)	494.00
Serotonin agonists	
Prucalopride (1-2 mg daily)	508.00
PAMORAs (for OIC only)	
Naldemedine (0.2 mg daily)	377.00
Naloxegol (12.5-25.0 mg daily)	427.00
Methylnaltrexone	
Subcutaneous (12 mg every other day)	2080.00
Oral (450 mg daily)	2079.00

Abbreviation: PAMORAs, peripheral µ-opioid antagonists.

[a] Approved for irritable bowel syndrome with constipation.

[b] Source: Lexi-Drugs Online (July 2019).

Managing OIC

The rapidly developing field of treatment for individuals with OIC was summarized in a 2019 guideline[8] that reduced the strength of supportive evidence to weak or nonexistent for 2 oral PAMORAs (alvimopan and methylnaltrexone) and added recommendations for the use of standard laxatives. A new oral PAMORA was approved for the management of OIC, and an oral form of methylnaltrexone is now available.

PAMORAs do not enter the central nervous system but inhibit only µ-opioid receptors in the gastrointestinal tract. Naloxegol, a pegylated form of naloxone, was the first PAMORA to be approved to manage OIC by the FDA in 2014, followed by methylnaltrexone, which is now available in both a subcutaneous injection form and as an oral agent. The latest PAMORA to become available is naldemedine, which is structurally related to naltrexone and was approved in 2017 by the FDA for the management of OIC.[9]

The data to support the use of naldemedine comes from 3 phase 3 randomized clinical trials including over 2400 patients. Adverse effects were higher in the active treatment groups but fell well below the threshold of clinically meaningful harm. It is the only PAMORA for which there is long-term (52 weeks) efficacy data available.

A 2019 guideline from the American Gastroenterological Association[9] contains recommendations for the management of OIC using GRADE (Grading of Recommendations Assessment, Development and Evaluation) definitions for strength of recommendations based on quality of evidence. The important conclusions are that (1) traditional laxatives should be used as first-line agents for the management of OIC because many patients respond to them, (2) PAMORAs should be considered only when traditional laxatives fail, and (3) there are strong recommendations based on moderately strong to strong quality of evidence for the use of naloxegol and naldemedine, whereas there is low quality of evidence for the use of methynaltrexone. The costs of naloxegol and naldemedine are substantially lower than that of methylnaltrexone (Table). Furthermore, there is insufficient evidence to support the use of lubiprostone and prucalopride for the management of OIC. These recommendations are similar to those proposed by the American Academy of Pain Medicine,[10] among other guidelines.

Summary

Traditional laxatives remain the first-line treatment for patients with OIC. There is a paucity of comparator studies and cost continues to be an important factor in choosing a treatment, as is the limited efficacy of some new agents. The PAMORAs naloxegol and naldemidine are far less costly than methylnaltrexone and their use is preferred based on moderately high-quality evidence on their efficacy and safety.

ARTICLE INFORMATION

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Published Online: November 4, 2019. doi:10.1001/jama.2019.16029

Conflict of Interest Disclosures: None reported.

Additional Contributions: Information on drug pricing from Lexi-Drugs Online was provided courtesy of Michael Hirsch, PharmD (Department of Pharmacy, University of Wisconsin Hospital and Clinics).

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