Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *Irritable Bowel Syndrome*
- May 2018 -

Background:

The National Pharmacy & Therapeutics Committee (NPTC) reviewed irritable bowel syndrome (IBS) and available treatment options at the May 2018 meeting. Prior to the review, the National Core Formulary (NCF) included two tricyclic antidepressants (TCAs) and two selective serotonin reuptake inhibitors (SSRIs), but no medications specifically indicated to treat this condition. After discussing the clinical data, pharmacoeconomic analyses and IHS utilization trends, **the NPTC added dicyclomine, loperamide, and polyethylene glycol (PEG) to the NCF**.

IBS is the most common functional gastrointestinal diagnosis, affecting as many as 10% of the North American population. It involves altered bowel habits and chronic abdominal pain. It is frequently episodic in nature and commonly has a significant detrimental effect on quality of life. The etiology is unclear but is likely multi-factorial involving possible factors such as stress, genetics, a disorder of the gut-brain axis, inflammation, alteration in microflora, and diet[1-5].

Discussion:

IBS is often a diagnosis of exclusion, due to similarities with other diseases, including inflammatory bowel disease, celiac disease, colon cancer, and food sensitivities/allergies. IBS is commonly classified as diarrhea predominant (IBS-D), constipation predominant (IBS-C), of mixed presentation (IBS-M), or un-typed, but is not to be confused with chronic idiopathic constipation which is not associated with pain[1,2,4-6].

Management options include pharmacologic and non-pharmacologic approaches (e.g., increased activity, scheduled relaxation time, peppermint oil, psychological therapy, and dietary changes). Pharmacologic options vary based on the predominant symptom and the main goals of treatment are to improve global IBS symptoms, decrease abdominal pain, and increase quality of life. Medications used to treat IBS-D include loperamide, alosetron, eluxadoline, SSRIs, TCAs, and rifaxamin. Treatment options for IBS-C include laxatives, linaclotide, lubiprostone, plecanatide and tegaserod. Antispasmodic agents and probiotics are used in all types of IBS[1,4,7-10].

The 2017 NICE Guidelines recommend antispasmodic agents, laxatives for constipation, and loperamide as first-line options for diarrhea. Second-line recommendations include linaclotide (after laxatives and with criteria), TCAs (if laxatives, loperamide, or antispasmodics are ineffective), and SSRIs (if TCAs not effective). For IBS-C, the American Gastroenterological Association (AGA) strongly recommends linaclotide and offers conditional recommendations for both lubiprostone and PEG. For IBS-D, the AGA recommends rifaxamin, alosetron, and loperamide while offering conditional recommendations for TCAs, SSRIs, and encourages the use of antispasmodics for more general IBS symptoms[7,9,10].

Loperamide, an antidiarrheal, has conflicting data in IBS-D treatment. Recent NICE guidelines list it as first-line antimotility agent, while the American College of Gastroenterology does not specifically recommend it due to a lack of evidence. While it may not achieve the goals of treatment, it can provide symptomatic relief for some patients[1,9].

Alosetron is a selective 5-hydroxytryptamine 3 (5-HT_3) receptor antagonist that inhibits sensory signals which lead to abdominal discomfort. A 2008 meta-analysis of RCTs found that as a class, 5-HT_3 receptor antagonists significantly improve abdominal pain and global symptoms in IBS-D, with a number needed to treat (NNT) for improvement in global IBS symptoms of 4. The NNT for relief of abdominal pain and discomfort was 7. The review took a comprehensive approach but may have been subject to publication and reporting bias. Another 2017 meta-analysis also found alosetron beneficial in treating IBS-D[11-13].

Eluxadoline is a mu-/kappa-opioid receptor agonist and delta-opioid receptor antagonist, leading to a constipating effect. It is a Schedule IV drug with numerous drug interactions. A 2017 meta-analysis reviewed 3 studies, finding that eluxadoline exhibited positive results in treating IBS-D symptoms[12,14].

Antidepressants including TCAs and SSRIS have also been utilized in treating IBS-D. TCAs, in particular, are thought to slow intestinal transit due to their anticholinergic effect. A 2013 Cochrane review found a beneficial effect for antidepressants (without focusing on a particular class) over placebo for improvement of abdominal pain (NNT=5), global assessment (NNT=4) and symptom score (NNT=4). A 2015 meta-analysis found that TCAs showed improvement in global symptoms and that SSRIs showed no statistically significant difference in global symptoms and no benefit regarding abdominal pain[1,15,16].

Antibiotics have long been considered as IBS treatment due to theories that an imbalance in the intestinal flora causes IBS symptoms. Usage has been limited due to possible side effects and concerns about potential drug resistance. Rifaxamin has been considered due to its very low oral absorption. A 2016 meta-analysis of RCTs found that overall symptom relief was greater in rifaxamin patients than placebo but that there was no significant difference in the relief of abdominal distension at the treatment endpoint or in abdominal pain. Dosing regimens, however, were highly variable, and reporting was subjective[1,17,18].

Laxatives are used in IBS-C for symptom relief. Among osmotic laxatives, PEG is more effective than lactulose (which is not recommended), improving constipation but not pain symptoms with minimal adverse effects. Stimulant laxatives have not been well studied[6].

Linaclotide and plecanatide are guanylate cyclase-C (GC-C) agonists. Activation of these receptors triggers a signal-transduction cascade, which induces intestinal chloride and fluid secretion leading to increased sodium and water in the intestinal lumen and accelerated intestinal transit. A 2017 meta-analysis found no difference in linaclotide and plecanatide, both were effective and well tolerated[12,19-21].

Lubiprostone activates type 2 chloride channels in intestinal epithelial cell apical membrane promoting secretion of chloride rich fluid and resulting in accelerated intestinal transit. In a 2016 meta-analysis, lubiprostone was determined to be both safe and effective with minimal side effects. Constipation severity was greater in lubiprostone-treated patients, though this was only significant at 1 week and 1 month[22].

Antispasmodics have long been used in treating IBS based on the assumption that smooth muscle spasm in the digestive tract contributes to IBS symptoms. A 2013 Cochrane Review of antispasmodics noted improvement of abdominal pain (NNT=7), global assessment (NNT=5) and symptom score (NNT=3)[8,15].

Similar to antibiotics, the potential benefit of probiotic use in IBS is tied to a possible alteration in gut bacteria. Though used extensively, little data is available to support or refute their benefit. Numerous available formulations pose challenges to interpreting the available data[8,9].

Findings:

IBS is highly prevalent and under-diagnosed. While numerous pharmacological agents are available, non-pharmacological treatment is at least as important. Etiology is often unclear, making IBS management challenging and successful treatment of IBS symptoms frequently a matter of trial and error.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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