



Pharmacological treatment of chronic constipation: a literature review

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ABSTRACT

Chronic constipation is a very common disease that is particularly commonplace among members of the elderly population. It is one of the most widespread bowel disorders, and it causes significant pain and discomfort; as such, it usually requires medical attention. The major causes of constipation are slow colonic movements and/or functional gastrointestinal disorders.

This review aimed to examine the pharmacological treatments that are currently available for chronic constipation. To develop insights into the causes and treatments of chronic constipation, relevant review articles that were published on the Pubmed, Cochrane database, and Embase websites, were examined. The outputs of these studies indicated that high daily intake of fibers and fluids in addition to regular exercise can be very helpful in avoiding and treating constipation. The pharmacological treatments that are administered to treat this disease typically increase the water content of the bowel lumen, and this leads to more regular bowel movements. Novel drugs have been introduced to treat constipation, and many of these are now subject to formal research studies. Since constipation can facilitate the development of other gastrointestinal diseases, it is important that we develop an understanding the therapeutic treatments that are available with the intention of identifying which of these may represent the most effective method for treating this disease. With that objective in mind, this review was undertaken to review the clinical effectiveness of the different pharmacological treatments that are employed to treat or prevent constipation.

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Introduction

Constipation, especially in chronic form, is one of the most common complaints among outpatients. In addition to being a local gastrointestinal tract problem, constipation may also be an etiologic factor in the development of other disorders. The large bowel and other organs can be directly and indirectly impacted by fecal toxins as a result of the retention of waste material during bouts of chronic constipation. The word constipation

has different meanings to different people. From the perspective of medical science, constipation is defined as less than three defecation incidents per week (1). The common symptoms of constipation are hardened stool, retained stool, failure to completely eliminate the stool, and/or the urge for defecation (2). Normal stool elimination frequency ranges from three times a day to three times a week (3). As such, the frequency of stool elimina-

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tion cannot be employed in isolation to diagnose constipation. The Rome system was established in 1991 to standardize the criteria employed to diagnose functional gastrointestinal disorders. In 2006, the Rome III criteria was introduced to categorize constipation. For a condition to be defined as constipation, it must meet at least two of the following factors:

1. Straining during 25% of defecation events;
2. Lumpy or hard stools in 25% of defecation events;
3. A sensation of incomplete evacuation in 25% of defecation events;
4. A sensation of anorectal obstruction in 25% of defecation events;
5. The need for manual maneuvers to facilitate 25% of defecation events; and
6. Fewer than three defecations per week (4).

In addition, people who suffer constipation seldom have loose stools without the use of laxatives and do not exhibit any signs of irritable bowel syndrome (5,6). For constipation to be viewed as chronic, the patient should have had the constipation symptoms for at least six months and have met the acceptable number of Rome III criteria for the last three of these months (6). The very high prevalence of constipation entails that it represents one of the top five diseases related to the gastrointestinal tract that have a significant impact on the quality of people's lives, especially the elderly. The prevalence of constipation in American society has been reported to be up to 27%, and the majority of affected people are elderly people who often have to take laxatives during the day. Elderly people are more likely to develop constipation because they have low intestinal motility and are more likely to take the various medicines that are linked with this disease (7,8). In addition, chronic constipation impacts women more than men (9). This review examines the various methods of treating chronic constipation that are available and evaluates their safety and efficacy.

Literature Review

Articles that were published in Pubmed, the Cochrane database, and Embase from the initiation of these databases until December 2014 were searched using a set of keywords: chronic constipation, clinical trial, and treatment. This search was complemented with a manual search of the references contained within the articles to identify any further studies that were of relevance to the research objectives. After collecting the articles, they were screened to identify those studies that described at least one therapeutic method for treating chronic constipation in people over the age of 18. The initial keyword search identi-

fied 130 articles. Duplicate articles were excluded and, according to the criteria described in the method section, 43 articles were subsequently included in the final review.

The Etiology of Chronic Constipation

-Extrinsic Factors

The most important factors that reduce intestinal motility are low consumption of fiber and fluids and low levels of physical activity. Low consumption of fiber and fluids can result from a lack of thirst, electrolyte abnormalities, metabolic disorders and/or consumption of certain medications, such as diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), anticholinergics, and/or beta-blockers (9-11).

-Intrinsic Factors

The internal factors that lead to chronic constipation fall into two categories (12,13): pelvic floor dysfunction (PFD) and slow colon transit time (STC). These factors do not operate completely independently of one another.

The complications of chronic constipation

-Anal fissure: A sudden split in the mucosa of the anal area when discharging hard stools can lead to anal fissures. The probability of this occurring is approximately five times greater when a patient is suffering from chronic constipation (14).

-Hemorrhoid: High pressure in the anal area due to the stool remaining in the colon for a long period of time can cause hemorrhoids.

-The prolapse of organs: The chronic high pressure that is placed on the pelvis during bouts of chronic constipation can predispose patients to rectum, bladder, uterus and vagina prolapse. The recurrence of these disorders is common in patients with chronic constipation (15).

-Perforation of the bowel: The hardened stool can exert pressure on the colonic wall. This can lead to the development of an ulcer followed by a hole in the colonic wall, which eventually causes peritonitis. This condition is not very common; however, it has led to death in some cases (16).

-Bowel obstruction: As a result of the stool being retained in the bowel for a long period of time it accumulates and hardens. This can eventually lead to the blockage of the large intestine. Surgery is usually needed to remedy this condition.

Diagnostic approach

Before administering any medication and performing physical examinations, it is important that medical professionals take a complete history of the patient. The diagnostic process that is employed can help to distinguish between a slow colonic transit time and pelvic floor dysfunction. A

colonoscopic approach should be considered if the patient has a history of colon cancer or irritable bowel syndrome and is exhibiting renal bleeding.

Methods of treatment

1) Lifestyle modification

Many of the current articles and studies that have studied chronic constipation emphasize the importance of diets that are rich in fluids and fibers in combination with exercise and physical activities (17). However, the role of these factors in the prevention and treatment of this disease has not yet been proven. A cohort study of 3327 women found that higher consumption of fiber decreases the occurrence of chronic constipation (18). However, some studies have indicated that there is no such association (19,20). A small randomized controlled trial indicated that regular exercise reduces the likelihood of chronic constipation, 88; however, an alternative, even smaller research study, did not agree with this finding. Two cohort studies have concurred that engaging in physical activity can reduce constipation in women (6). Furthermore, according to one controlled trial, higher fluid intake accompanied by a diet that is high in fiber has also been found to reduce cases of chronic constipation (21).

2) Pharmacological treatments

The pharmacological treatments that are available for chronic constipation can be categorized into the following groups.

2.1) Bulk forming agents

This medicine category includes fiber supplements, which are considered as the first-line therapy for chronic constipation disease. These substances expand in the presence of water, increase the stool bulk, and stimulate defecation. The products of this category, which are available in industrial forms, include psyllium seeds, methylcellulose, and bran. For these medications to be effective, it is critical that the patient consumes large amounts of fluid. If the patient does not consume sufficient water, these substances will expand and cause further bowel obstruction as opposed to remedying it. Of the drugs that are available in this category, psyllium has been found to treat constipation with the highest degree of efficiency because it reduces colonic transit time as well as enhancing the solidity and/or hardness of the stool (22,23).

2.2) Emollients and stool softeners

Mineral oil is known to have emollient effects on a stool and, as such, it is often used in the treatment of chronic constipation. However, no valid clinical

trial has been performed that has compared the effect of mineral oil in comparison to that of a placebo. One of the complications and risks associated with the use of this medicine in children and elderly people is the occurrence of aspiration and lipid pneumonia. As such, it is only prescribed at a moderate level (24,25). Docusate sodium is a further substance that is believed to act as an emollient and stool softener, and it has the added advantage that it demonstrates detergent effects. Although no study has compared the use of this substance in isolation with that of a placebo, a double-blind randomized clinical trial did find that this substance was preferable to psyllium for the treatment of chronic constipation. According to the studies conducted, the use of this substance is recommended at a moderate level (22). This category of medicines is used when bulk-forming agents are not very effective and/or their use is not suitable for a given patient.

2.3) Osmotic agents

This category includes medicines such as lactulose, sorbitol, polyethylene glycols, and magnesium hydroxide. These substances operate by absorbing water and making the stool progress more smoothly through the digestive system. Lactulose has been proven to be particularly effective, and clinical trials have found that it has a positive effect when compared with a placebo (26,27). Studies have also been conducted to compare sorbitol and lactulose and have found no major differences between the two medications (28). Polyethylene glycols are among the substances that have been proven to increase the frequency and softness of the stool when compared to a placebo in at least three clinical trials. Nevertheless, there are a number of complications associated with this medicine; for example, negative side effects such as nausea, flatulence, and diarrhea. These should be taken into consideration, especially when it is prescribed to the elderly (9,29). This category of medicines will typically be prescribed in cases in which the first two categories of medication are not appropriate.

2.4) Stimulants

Senna and bisacodyl are the most common types of stimulants. These medicines increase colonic peristaltic contractions but reduce transit time. They also reduce the absorption of water from the lumen (30). Bisacodyl is the most commonly used medicine in this category. In connection with bisacodyl, several double-blind randomized clinical trials have demonstrated its efficacy and efficiency compared to that of a placebo (31). At least three studies have been performed that compared the

effects of Senna with that of another laxative in the treatment of chronic constipation, and/or suggested its combined use (32). However, there is no RCT study that compares its efficacy with that of a placebo. There is some evidence to suggest that the long-term use of Senna may result in colon cancer; as such, Senna should only be used at a moderate level.

2.5) Chloride channel activators

This category of medicines is bicyclic fatty acids that increase fluid secretion through activating type 2 chloride channels in the gastrointestinal epithelial membrane. Lubiprostone is one medication that falls into this category. It was approved by the US Food and Drug Administration in 2006 for the long-term treatment of chronic constipation (33,34). At least three clinical trials have reported the efficiency with which this medicine improves the symptoms of chronic constipation (35). According to the studies conducted, this medication can be safely used on a long-term basis (36). Although it is associated with the side effects of headaches, nausea, and diarrhea, in general, this medicine is well tolerated.

2.6) 5- Hydroxytryptamine receptor (subtype 4) agonist (5-HT4)

The 5-HT₄ receptors can be found in some of the cellular structures involved in bowel motility such as smooth muscle cells and neurons. In fact, these substances mediate the release of other neurotransmitters that play a role in initiating intestinal peristaltic movements (37). Tegaserod, one of the medicines that are common in this category, is a 5-HT₄ receptor agonist that was produced in 2002 with the aim of easing constipation. It has since also been approved for use in patients with IBS as well as for the treatment of idiopathic constipation in people who are aged below 65 years of age. Although several randomized clinical trials have proven the efficiency of this medicine, in 2007, the FDA prohibited its consumption due to its links with cardiovascular disease (38). Studies on this medicine are still continuing, and the two cohort studies that have recently been conducted have not shown any relationship between cardiovascular disorders and this medicine (39).

2.7) Guanylate cyclase-c receptor agonist

Intestinal fluid secretion is triggered by the stimulation of Guanylate cyclase-c receptors of colonic epithelium. Linaclotide (a 14 amino acid peptide) is one of the stimulant factors that affects these receptors. The efficiency and safety of this medicine have been investigated in several clinical trials (40).

3) Other treatments

Probiotics, Lactobacillus, and Bifidobacterium are found in the normal flora of the large intestine. They compete with harmful pathogens to bind to the surface of enterocytes, and they also maintain the health of mucus. Patients who are suffering from chronic constipation typically have a lack of this bacteria in their large intestine (41). Therefore, the use of probiotics can be necessary to treat chronic constipation and other inflammatory conditions (42). Unfortunately, due to the small number of clinical trials that have been conducted, there are very few recommendations available on how these products should be prescribed.

4) Surgery

Patients who suffer from slow chronic transit constipation and who have not been cured by pharmacological treatments sometimes require surgery. This surgery can include a complete or partial colectomy. Based on a review study, performing such surgery can reduce the use of laxatives and improve the frequency of stools, even though more studies are needed to prove this (43).

Conclusion

Chronic constipation is a common disease that occurs in at least one-quarter of the population. It can be treated through different methods. One important method of treating this disease is by increasing fiber and fluid in the diet and engaging in physical activity on a more frequent basis. The best pharmacological method for treating chronic constipation is the use of bulk-forming agents, such as psyllium seeds, along with stool softeners and/or osmotic agents. If untreated, stimulants will also be added to this therapeutic method. Finally, more novel should be considered. In highly resistant cases, surgery may be required.

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Conflict of Interest

The authors declare no conflict of interest.

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