

# Chronic constipation and treatment options (Review)

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**Abstract.** Chronic constipation (CC) is a highly prevalent heterogeneous disorder. Although CC is not known to be associated with the development of serious disease or with excess mortality, it considerably reduces the patients quality of life. In addition, it represents an economic burden to patients and society. The majority of patients with CC successfully manage the disorder by dietary management and the use of laxatives. Patients with functional CC (slow-transit and non-slow transit constipation) do not respond to laxatives and are a small fraction of the total population complaining of constipation. Regardless of the low number of these patients, the intractability of their symptoms causes psychological and social stress and greatly impairs their quality of life. Furthermore, these patients consume a disproportionate quantity of medical resources. It appears that these patients have a disturbance in the serotonin transmission system, which results in a cascade of alterations in a number of gut neuroendocrine hormones/transmitters. The effect of prucalopride, a serotonin receptor agonist, in this category of patients appears to be not only a pharmacological prokinetic action, but also a correction of a pre-existing disturbance. Linaclotide, a member of the guanylin peptide family, binds to the ligand-binding region of guanylate cyclase-C on the luminal surface of gastrointestinal epithelia resulting in increased fluid secretion. This drug has also been found to be effective for the treatment of functional CC. In addition, biofeedback and sacral nerve stimulation are effective in the treatment of CC caused by pelvic floor disorders.

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## 1. Introduction

Chronic constipation (CC) is a highly prevalent heterogeneous disorder. The prevalence of CC varies based on how the disorder is defined and whether CC is self-reported or based on criteria (1-5) (Fig. 1). The prevalence rates for females are almost double those for males. CC is not known to be associated with the development of serious disease or with excess mortality rate. However, CC considerably reduces the quality of life to the same degree or more severe than impairments caused by a number of other chronic diseases, including arthritis, asthma or coronary artery disease (6-9). CC is commonly associated with anxiety and depression worldwide (10-12).

In addition to the increased morbidity caused by CC, it is an economic burden to the patients and society. Significant economic costs in CC arise from direct and indirect costs. The direct costs are associated with evaluation and treatment and the indirect costs are caused by missing school or work (absenteeism) or not being as productive at school or work as usual (presenteeism). CC led to 6.3 million patient visits in the US in 2004 (13,14). A large survey study found that the annual health care costs for patients with CC were US\$7522 per patient, ~50% higher compared with patients with irritable bowel syndrome (IBS; US\$5049 per patient) (11). The long-term direct medical costs of CC are double those of controls over a 15-year period (US\$63,591 vs. \$24,529) (15). In England, 14 million prescriptions were issued for laxatives per year at a cost of £60 million (1).

## 2. Definition and types of constipation

Constipation is a complex symptom that may be clinically grouped into infrequent bowel movements (<3 per week) and difficult defecation, including straining at defecation, hard or lumpy stools, sensation of incomplete evacuation, sensation of

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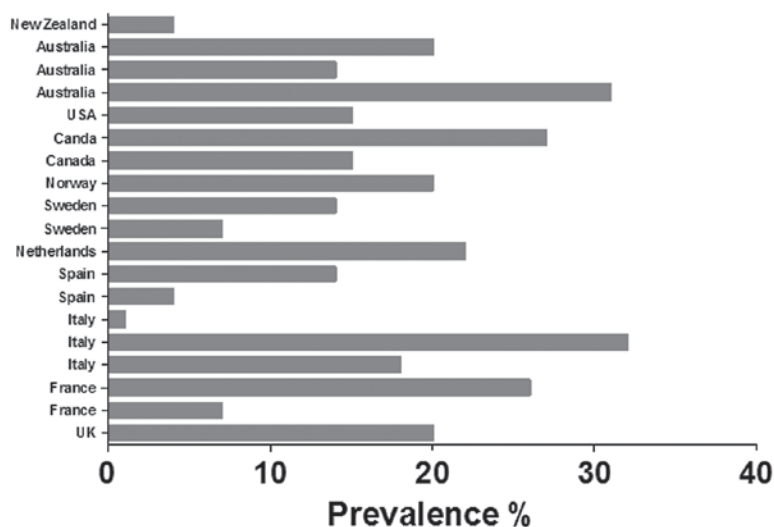


Figure 1. Prevalence of constipation in various countries.

blockage or anorectal obstruction and manual manoeuvres to defecation.

As mentioned previously, patients with CC are a heterogeneous group and may be roughly divided into 3 groups: i) Constipation in the elderly and cancer patients; ii) constipation associated with neuromuscular diseases and iii) functional constipation.

Constipation in the elderly and cancer patients constitutes the majority of CC patients. Neither motility disturbances in the gastrointestinal tract or abnormalities in the gut neuroendocrine system have been described to be associated with aging (16-18). It appears that constipation in the elderly is caused primarily by co-morbidity and the side effects of drugs, particularly those used against cardiovascular diseases. In cancer patients, constipation is caused mainly by opiates.

Patients with neuromuscular diseases, including Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis suffer from chronic constipation, which is treated differently.

Functional CC comprises idiopathic chronic slow transit constipation and severe forms of IBS. A number of gastroenterologists, including the authors, believe that they are variants of the same disorder (19).

### 3. Possible mechanisms for functional constipation

A number of abnormalities in the neuroendocrine system (NES) of the gut have been observed in slow transit and non-slow transit (IBS-constipation?) (20-30). The gut NES is a local regulatory system, that controls numerous functions of the gastrointestinal tract, including motility, secretion, absorption, gut microcirculation, local immune defence and cell proliferation. It consists of two parts: i) Endocrine cells spread between the epithelial cells of the mucosa facing the gut lumen and ii) peptidergic, serotonergic and nitric-oxide-containing nerves of the enteric nervous system in the gut wall. The gut NES is operated by a large number of bioactive messengers that exert their effects via endocrine, paracrine and neuroendocrine modes of action or by synaptic signalling (31,32). The

different components of this system interact and integrate with each other and with the afferent and efferent nerve fibres of the central nervous system (33,34).

In slow and non-slow transit constipation low colonic serotonin and peptide YY (PYY) cell densities and low serotonin content have been observed (24,26,30,33) (Figs. 2 and 3). Serotonin activates the submucosal sensory branch of the enteric nervous system (32,34), which conveys sensations to the central nervous system that are likely to generate the sensation of abdominal pain/discomfort. Furthermore, serotonin controls gastrointestinal motility and chloride secretion via interneurons and motor neurons (31,34). PYY stimulates the absorption of water and electrolytes and is a major regulator of the 'ileal brake'. Furthermore, PYY inhibits prostaglandin E2 and vasoactive intestinal polypeptides, which stimulate intestinal fluid secretion (32,34). Administration of PYY inhibits diarrhoea in experimental mouse models by reducing intestinal fluid secretion and slowing colonic transit (32,34). It appears that functional CC patients have a disturbance in the serotonin transmission system, which causes a cascade of changes in a number of gut neuroendocrine hormones/transmitters, the most important of which is PYY.

### 4. Treatment options

The European guidelines recommend a treatment algorithm for CC (Fig. 4) (35). The drugs used for the treatment of constipation are summarized in Table I.

Non-pharmacological and changes in life style are the first approaches in the management of mild and moderate constipation. Guidance of diet management with an emphasis on an increase in soluble fibre intake appears to be effective in patients with mild and moderate constipation (35). Based on clinical experience and circumstantial evidence, physicians recommend exercise for CC patients. The physical activity effects on CC patients have previously been attributed to promoting overall wellbeing. However, physical activity has been found recently to increase gastrointestinal transit (36-39). The increased gastrointestinal motility has been attributed to vagus stimulation and/or

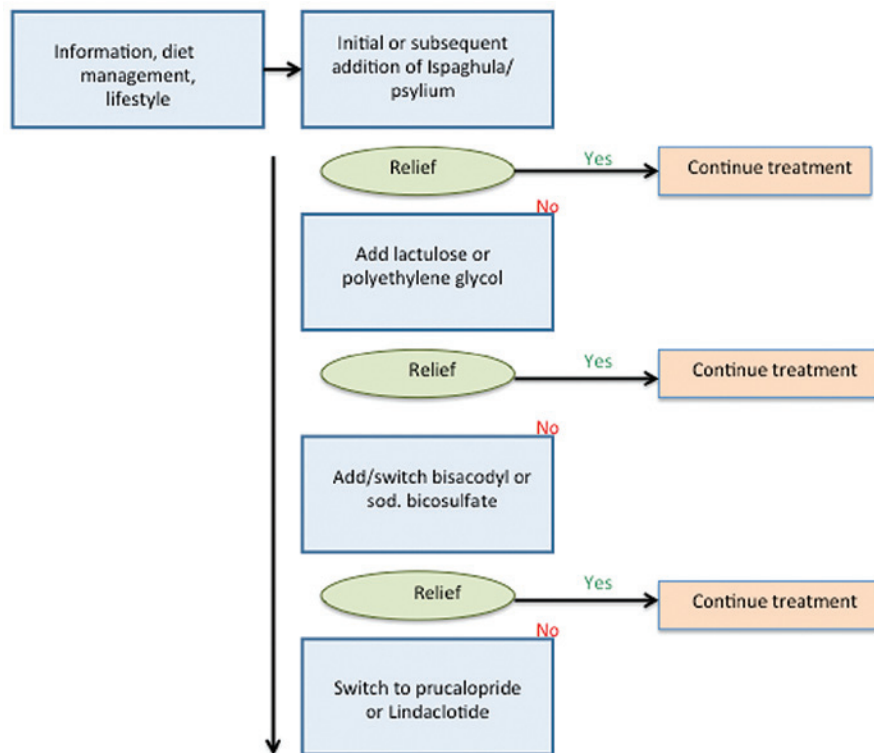


Figure 2. Treatment algorithm used in Norway for chronic constipation.

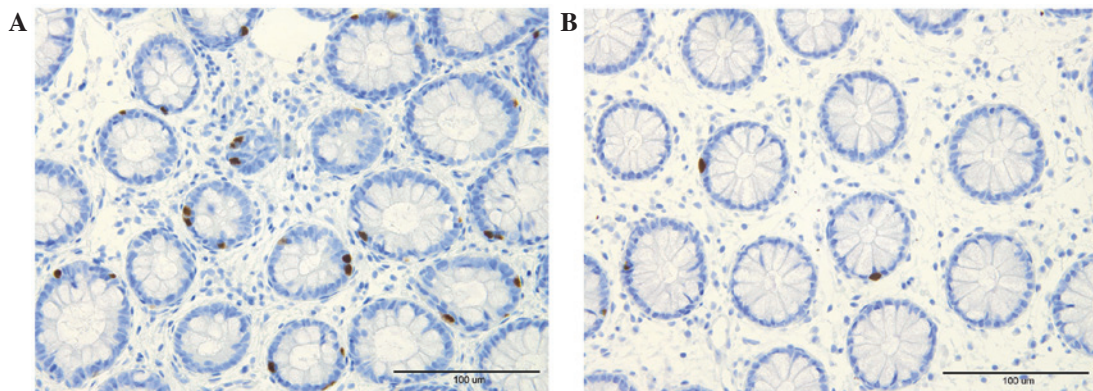


Figure 3. Serotonin immunoreactive cells in the colon of a subject who underwent colonoscopy due to gastrointestinal bleeding, where the cause of bleeding was identified as angiodysplasia (A) and in a patient with slow transit constipation (B).

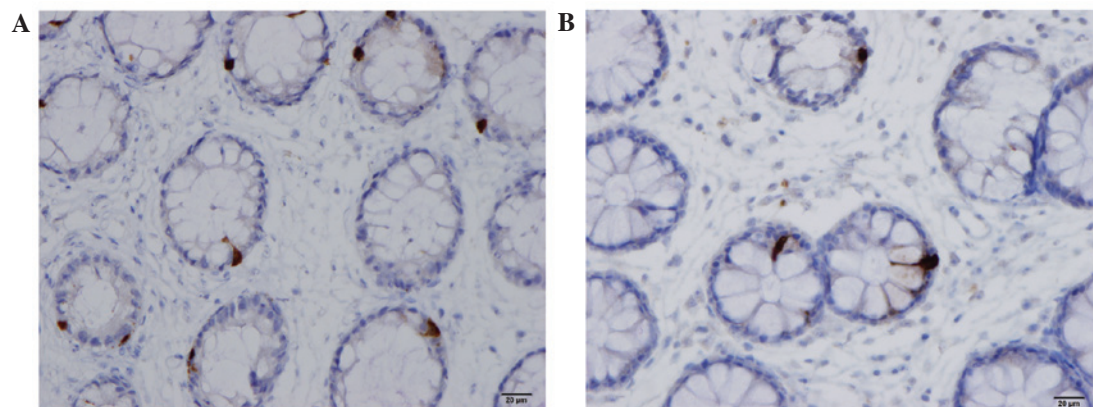


Figure 4. PYY in the colon of a subject who underwent colonoscopy due to gastrointestinal bleeding, where the cause of bleeding was identified as haemorrhoids (A) and in a patient with irritable bowel syndrome with constipation as a predominant symptom (B). PYY, Polypeptide YY.

Table I. The most common types of drugs used for the treatment of patients with chronic constipation.

Drug class	Generic name	Comments	Dose
Bulking agents	Psyllium	Effective	25-30 g daily in divided doses
	Ispaghula	Effective	3.5 g one to three times daily
Osmotic laxative	Polyethylene glycol	Effective Unpalatable taste	17 g in 237 ml solution daily
	Lactulose	Effective May cause bloating, flatulence and cramping	15-30 ml (667 mg/ml) daily
Stimulant laxatives	Bisacodyl	Effective, but the effects subside with time, can cause cramping	5-20 mg daily
	Natrium bicosulfate		5-10 mg daily
Emollient laxative	Mineral oil	Effective	5-10 cm <sup>3</sup> daily
	Glycerine suppositories	Effective Initiates evacuation by distending the rectum	On demand
Prokinetic and prosecretory agents	Pruclopride	Effective. May cause headache, nausea, abdominal pain and diarrhoea. These adverse events occur within the first 24 h of treatment and are short lived	2 mg daily
	Linaclotide	Effective Diarrhea is the most common side effect	290 µg daily

decreased blood flow to the gut, which leads to an increase in important gastrointestinal hormone release (39). Probiotic intake has also been shown to improve CC symptoms depending on the preparation used and a number of products appear to be more effective than others (40-44). The bacteria that have been proven to be effective in this aspect are *Bifidobacterium infantis* 35624, *Bifidobacterium lactis* DN-173-010, *Lactobacillus plantum*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus* and *Streptococcus faecium* (41-44). The mechanism that appears to underlie this improvement is the ability of these bacteria to reduce the number of sulphite-reducing *Clostridia* spp., which is known to produce gas upon the fermentation of nutrients. This may contribute to improvements in flatulence, bloating and abdominal distension in CC patients (42). Combining diet management, regular exercise and probiotics intake has been found to be effective in reducing the symptoms and improving the quality of life in CC patients with mild and moderate symptoms (45).

In the elderly, concomitant drug use should be assessed and drugs that potentially cause constipation should be discontinued, when possible. Constipation in the elderly and in cancer patients is treated successfully by using one or more of the following bulking agents; polyethylene glycol, lactulose, sodium bicosulphate and bisacodyl. Probiotic intake reduces the side effects of lactulose and fibres. CC in patients with neuromuscular diseases is successfully treated with polyethylene glycol.

Patients with functional CC do not respond to any of the laxatives mentioned previously. They are a small fraction of the total population complaining of constipation (46). Regardless of the low number of these patients, the intractability of their symptoms causes psychological and social stress and greatly impairs their quality of life. Furthermore, they consume a

disproportionate quantity of medical resources. The treatment options for these patients are prucalopride, linaclotide, biofeedback and sacral nerve stimulation.

Prucalopride is a highly selective serotonin 5HT<sub>4</sub> receptor agonist that has been shown to stimulate gut motility (47). It has been observed to be effective in the treatment of CC that does not respond to laxatives (47-51). Furthermore, it is safe for use in the elderly who commonly suffer from cardiovascular diseases (47-51). As mentioned previously, patients with CC have low serotonin content in the large intestine and it is possible that the effects of prucalopride, a serotonin receptor agonist in this category of patients is not only a pharmacological prokinetic effect, but also a correction of a pre-existing defect in serotonin.

Linaclotide is a member of the guanylin peptide family and similar to endogenous peptide hormones, guanylin and uroguanylin have been shown to bind to the ligand binding region of guanylate cyclase-C on the luminal surface of gastrointestinal epithelia, resulting in increased fluid secretion (52). Moreover, linaclotide has been observed to accelerate gastrointestinal transit (52) and has been found to be effective in the treatment of functional CC.

Biofeedback and sacral nerve stimulation have a limited availability and content of biofeedback treatment varies among centers. These treatments are effective in constipation caused by pelvic floor disorders, but the author's observations and recently published reports showed that this treatment is not effective in functional constipation (53).

## 5. Conclusion

CC is a common gastrointestinal disorder with different aetiology. It markedly reduces the patient's quality of life and is



an economic burden to the patients and society. The majority of patients are treated successfully with changes in life style, bulking agents or other laxatives. Patients with functional CC who do not respond to the treatment with laxatives may be treated with prucaloprid or linaclotide. Patients with CC caused by pelvic floor disorders may be successfully treated by biofeedback or sacral nerve stimulation

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