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## Constipation—modern laxative therapy

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**Abstract** It is estimated that one third of the population in Western industrial countries suffers from constipation at least from time to time. Constipation may have somatopathic or functional causes. Furthermore, a great number of substances are known to cause medication-induced constipation, i.e. opioid-induced constipation is caused by linkage of the opioid to opioid receptors in the bowel and the central nerve system. Whenever possible, causal therapy should be undertaken. Patients in palliative care mostly suffer from chronic functional constipation. The treatment consists of basic measures and the application of laxatives. According to their mode of action, they are divided into bulk-forming laxatives, osmotic laxatives, stimulant laxatives, lubricating agents and others. Bulk-forming laxatives are not recommended for use in palliative care patients, for such patients are normally not able to take in the required amount of fluids. Osmotic laxatives are divided into (magnesium) salts, saccharine, alcohols and macrogols. Lactulose is the most popular saccharine laxative. Because of its side effects (flatulence, bloating and

abdominal cramping), lactulose is not a laxative of our choice; instead, we prefer to give macrogol. Orally administered, macrogol is not metabolised and pH value and bowel flora remain unchanged. Macrogol hydrates hardened stools, increases stool volume, decreases the duration of colon passage and dilates the bowel wall that then triggers the defecation reflex. Even when given for some time, the effectiveness of macrogol will not decrease. Because of its high effectiveness and commonly good tolerance, macrogol has become the laxative of first choice in palliative care patients with all kinds of chronic constipation, if these patients are able to take in the necessary amount of fluids. From the general medical point of view, lubricating agents have become obsolete. In palliative care patients, however, they are still important laxatives for prophylactic treatment or therapy of constipation. Due to clinical experience, in palliative care a laxative ladder has proven successful.

**Keywords** Constipation · Physiology · Therapy · Laxatives · Opioids · Palliative medicine

### Introduction

To date there has been no international consensus on a general definition and classification of constipation. Any definition that is, for example, based purely on the frequency of bowel movements does not do justice to the

majority of patients who claim to suffer from constipation. The term constipation indicates a subjective impression that:

- The frequency of bowel movements is dissatisfying
- There is a sensation of incomplete evacuation

- The consistency of the stool is too hard and/or
- The stool is passed with discomfort [12].

Indications for constipation are given when there are less than three bowel movements per week, less than 35 g of stool per day, stool water weight is less than 70% and gastrointestinal transit time is longer than five days [3].

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## Epidemiology

It is estimated that one third of the population in Western industrial countries suffers from constipation at least occasionally. We know that constipation occurs more often in women and that the incidence of constipation increases with age [5, 11, 14, 15, 17].

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## Causes of constipation

The possible causes of constipation are manifold, but they may be subsumed under two main categories, which are:

1. Somatopathic causes
2. Functional causes.

Somatopathic constipation may be a result of diseases such as diverticulitis, tumours/cancer, inflammatory processes in the anal area, neurological diseases, endocrinal diseases, recto-anal diseases or metabolic changes. Functional constipation may be due to a prolonged colon passage, defecation disorder, poor intake of fluids or dietary fibres, medication or situational factors such as way of life, lack of exercise/immobility.

A large number of substances are known to cause medication-induced constipation, i.e. antacids, antibiotics, anticholinergics, antihypertensives, anticonvulsants, anti-Parkinsonian medications, diuretics, excessive use of laxatives, muscle relaxants, neuroleptics, non-steroidal antiphlogistics, opioids and many others.

### Opioid-induced constipation

Constipation is the most frequent and most persistent side effect of opioid treatment [7, 16, 18]. Unlike other side effects of opioid medication, such as nausea and emesis, there is no, or extremely slow, tolerance build-up to the constipatory effects of opioids. Therefore, patients tend to require regular laxative treatment for the duration of the opioid therapy.

### Causes and pathophysiology of opioid-induced constipation

Peripheral as well as intrathecal and intraventricular application of opioids will lead to a prolonged colon pas-

sage of the bowel content due to the fact that opioid-induced constipation is caused by linkage of the opioid to opioid receptors in the bowel and the central nervous system [6, 7].

The inhibition of release of acetylcholine from the myenteric plexus leads to a relaxation of the longitudinal musculature of the colon and small intestine. Subsequently, the propulsive motor function decreases. Furthermore, opioids cause an increase of segmental intestinal contractions. Therefore, the faeces stay in the intestine for longer, leading to a withdrawal of water and a thickening and lengthening of the stool.

Furthermore, intestinal, gastric, biliary and pancreatic secretions are decreased. Hyperactivity of the tonus of the intestinal sphincters and an impaired defecation reflex add to the constipatory effect.

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## Diagnostics

Basic diagnostic measures include patient history, medical examination including inspection of the anal area, digital examination of the sphincter muscles and the rectum, stool examination and laboratory tests. Questions regarding the patient's history should include issues such as:

- Beginning and duration of constipation
- Pain in the abdominal area or during defecation
- Sensation of fullness
- Diet and eating habits
- Medication
- Sensation of incomplete evacuation
- Stool consistency
- Stool colour
- Use of laxatives.

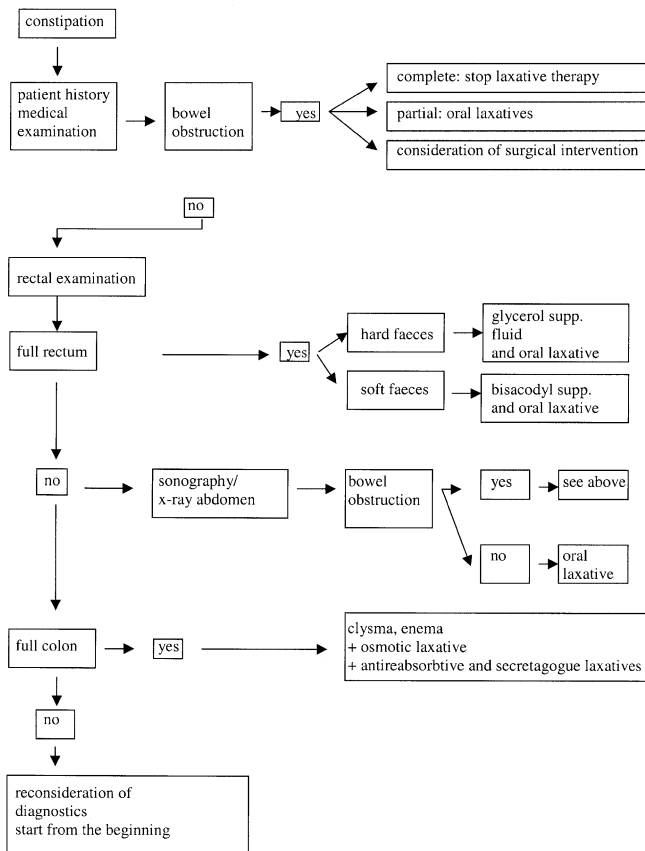
Details regarding these basic diagnostic measures, as well as details regarding measures such as sonography, X-ray and colonoscopy, are beyond the scope of this paper.

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## Therapy

### General measures

Whenever possible, causal therapy should be undertaken. The flow diagram (see Fig. 1) shows a systematic regimen for the assessment of an adequate strategy. If constipation is suspected, the first step must be to examine whether the patient suffers from gastrointestinal obstruction. If this is the case, the next step is to assess whether this gastrointestinal obstruction is complete or incomplete. In the case of complete gastrointestinal obstruction, no laxatives must be given, where-



**Fig. 1** Flow diagram: diagnosis and therapy of constipation in palliative care patients

as they are indicated in the case of incomplete obstruction. Furthermore, the pros and cons of a potential surgical intervention should be weighed up in either case.

If a gastrointestinal obstruction has been eliminated, a rectal medical examination may reveal information for further diagnostic measures. If the rectum is full and the faeces are of a soft consistency, a stimulating suppository should be given in tandem with oral administration of a laxative, i.e. macrogol. If the faeces are hard, a stool-softening suppository in tandem with orally taken fluid and a laxative are indicated.

If the rectum is empty, the possibility of an obstruction must be considered, i.e. eliminated. An empty rectum but a full colon is an indication for the application of a clysmas or enema in combination with oral administration of an osmotic laxative and stimulants. If both the rectum and colon are empty, other diagnostic measures must be considered.

Palliative care patients most frequently suffer from chronic functional constipation, the treatment of which includes basic therapeutic measures and the administration of laxatives.

## Basic measures

### Basic therapeutic measures include:

- Information about the symptom complex, pathophysiology and potential causes of constipation
- Information about physiotherapeutic measures
- Increasing exercise
- Increasing dietary fibre intake (to approximately 20–35 g/d)
- Increasing intake of fluids (to about 1.5–2l/d).

However, palliative care patients are rarely able to undertake these important and effective basic measures, as most of them suffer from increasing fatigue, immobility and loss of appetite. Therefore, there is a clear medical indication for the application of laxatives.

## Laxatives

Laxatives are substances that accelerate defecation. They have an impact on the transfer of water and electrolytes of the small and large intestinal mucosa, and they soften hardened faeces and stimulate defecation. According to their mode of action, they are divided into:

- Bulk-forming laxatives
- Osmotic laxatives
- Stimulant laxatives
- Lubricating agents
- Others.

### Bulk-forming laxatives

Chemically, bulk-forming laxatives are divided into different substances, which have in common that they cannot be broken down and are therefore only marginally absorbed, if at all. Mostly, they consist of natural or synthetic polysaccharides. By absorbing water in the intestine, bulk-forming laxatives increase the volume and softness of faeces, thus dilating the intestinal wall, which subsequently increases the propulsive motor function.

The use of bulk-forming laxatives in palliative care patients is not recommended, for these patients are usually confined to bed and cannot take in the required amount of fluids.

### Osmotic laxatives

The substance group of osmotic laxatives is heterogeneous. The common denominator of osmotic laxatives is that they are not—or only marginally—reabsorbed during the bowel transit. Water taken in as a component of

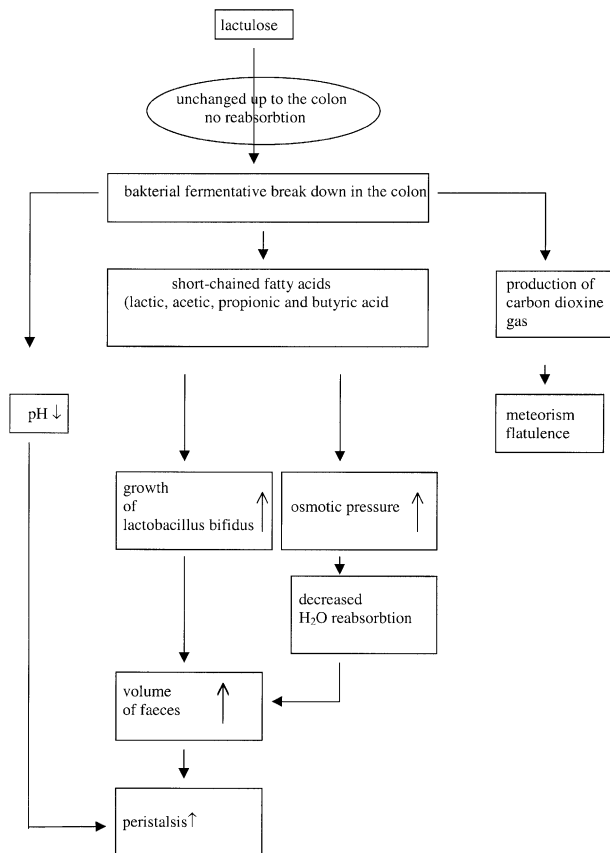


Fig. 2 Mode of action of lactulose

food remains bound and is transferred to the extracellular space in the bowel. Osmotic laxatives are divided into (magnesium) salts, saccharine, alcohols and macrogols. The following focuses on saccharine laxatives and macrogols only.

#### Saccharine laxatives

Lactulose is a disaccharide, consisting of glucose and fructose that cannot be broken down in the small intestine (see Fig. 2). Lactulose passes the gastrointestinal tract unabsorbed as far as the colon, where bacteria break down the sugar into short-chained fatty acids. Subsequently, the intraluminal pH value decreases, which causes an increase of peristaltic movements. Furthermore, the osmotic pressure in the colon lumen increases and water is retained in the intestine. The stool softens and increases in volume. Therefore, the bowel wall dilates, which then triggers the reflex action of the bowel peristalsis. Common side effects of lactulose are flatulence, abdominal cramps and bloating.

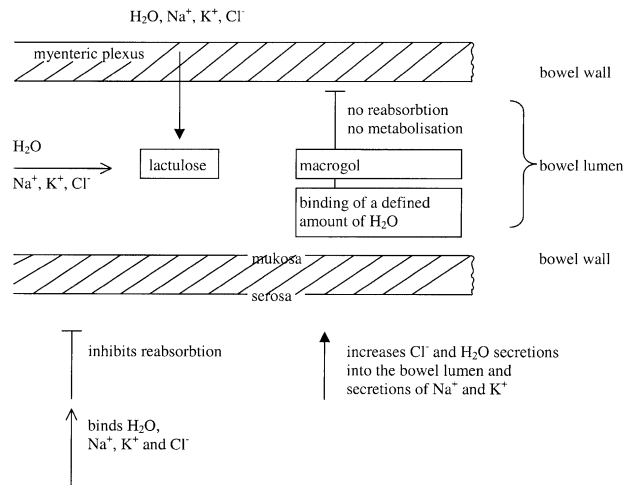


Fig. 3 Mode of action of lactulose and macrogol (mod. Müller-Lissner [13])

#### Polyethylene glycol (macrogol)

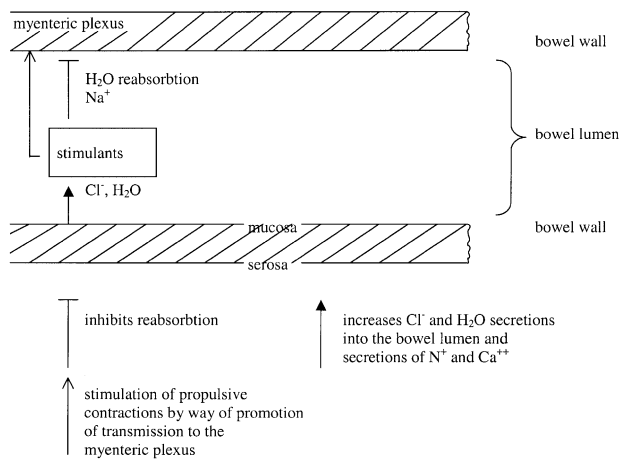
Originally, polyethylene glycol was given in relatively high doses in order to induce purgation, i.e. as a preparatory measure for gastroenterologic interventions such as colonoscopy [4]. Orally administered, macrogol is not metabolised—i.e. there is no bacterial or enzymatic metabolism—pH value and bowel flora remain unchanged and there is no fermentative production of intestinal gas (see Fig. 3).

Not only is the water-binding capacity of macrogol exactly defined, it also does not lead to a loss of fluids and electrolytes because it only binds orally taken fluid [1].

Macrogol hydrates hardened stools, increases stool volume, decreases the duration of the colon passage and dilates the bowel wall, which then triggers the defecation reflex. The relation between dosage and effect is linear. Macrogol draws no water from the body and therefore shows a neutral balance. The effectiveness of macrogol does not decrease over time [2, 4, 8, 9]. Furthermore, its effectiveness is independent of both time of application (i.e. time of day) and time of food intake. After the first application, the initial effect is seen in 2 to 3 days. If taken regularly, the frequency of bowel movements tends to be one movement per day.

Because of its high effectiveness and good tolerance, macrogol has become the laxative of choice for palliative care patients with all kinds of chronic constipation and opioid-induced constipation, provided that these patients are able to take in the necessary amount of fluids (125 ml fluids per sachet).

Compared with the administration of lactulose, side effects occur much less frequently, in particular, the above-mentioned and very common flatulence, bloating and abdominal cramps.



**Fig. 4** Mode of action of stimulant laxatives

### Stimulants (antireabsorptive and secretagogue acting agents)

Antireabsorptive and secretagogue acting agents inhibit the reabsorption of liquid and sodium from the bowel lumen. Furthermore, they induce an inflow of sodium, chloride, calcium and liquid into the bowel lumen, and the sennosides increase the propulsive motor function due to their direct effect on the myenteric plexus (see Fig. 4). Stimulants include:

- Anthracenes
- Diphenols (phenolphthalein, bisacodyl, sodium picosulphate)
- Fatty acids

The group of anthracenes includes senna preparations, which are reliable and effective laxatives. However, it has to be mentioned that they can cause cramp-like intestinal pain. Diphenols include bisacodyl and sodium picosulphate; the latter in particular is often used in palliative care patients. Castor oil (*ricini oleum*, Ph. Eur) belongs to the group of fatty acids. The special effect of castor oil is that it—unlike most other laxatives—enhances the peristaltic movement, even in the small intestine. Its laxative effect may be described as drastic, often accompanied with cramp-like abdominal pain. Therefore, castor oil can only be recommended for certain indications.

### Lubricants

Lubricating agents are stool softeners and ease defecation due to their surfactant effect. This substance group includes non-reabsorbable oils, oils that are very difficult to reabsorb such as paraffin. Because of some side effects, lubricating agents are regarded as obsolete. In pal-

liative care patients, however, they remain important agents for the prevention and treatment of constipation.

### Other laxatives

Other laxative agents include prokinetics, metoprolamide, erythromycin, misoprostol and opioid antagonists. There is evidence that opioid antagonists (i.e. naloxone, orally administered, 8–10 mg/d) resolve opioid-induced constipation without having a negative impact on the analgetic effect of the opioid due to a displacement of the opioid from the intestinal opioid receptors [10, 16]. The analgetic effect of the opioid remains unchanged because of the high first-pass effect of naloxone.

### Rectal laxatives

Rectal laxatives include suppositories, clysmas and enema preparations. Suppositories and clysmas contain mono-substances or combinations of secretagogue-acting agents or stool softeners for rectal application, i.e. bisacodyl, glycerol, sorbitol and docusate sodium. An enema is the application of larger amounts of fluids into the rectum, a high enema is used to reach as many segments of the colon as possible. The effect of the enema depends on:

- The amount of applied fluid
- The intraluminal pressure
- The temperature of the enema
- Additional substances such as glycerol, olive oil, sodium chloride and others.

### Assessment of clinical use

Before any therapeutic measures can be implemented, a diagnosis must be undertaken based on a full holistic assessment as to whether the existing constipation is an independent syndrome, a symptom of a disease or possibly due to exogenic factors such as intake of medication with constipatory effects. Physicians must exclude organic or other constipation for which a causal treatment would be appropriate. Basic treatment of constipation includes:

- Information for the patient about the nature, cause and options for the treatment of constipation
- Promotion of exercise
- Intake of an adequate amount of dietary fibres in order to enhance the water-binding capacity of the faeces
- Intake of a diet that serves to promote bowel motility, i.e. fruit, dates, salad



- Intake of the required amount of fluid (at least 1.5l/d)
- Avoidance of constipation-promoting food (such as refined flour products, chocolate, bananas, tea other than herbal or fruit, etc).

These generally effective basic measures, however, are rarely applicable to palliative care patients, as most of them suffer increasingly from:

- Increasing fatigue
- Immobility and confinement to bed
- Loss of appetite and aversion to a fibre rich diet
- Decreasing intake of fluid.

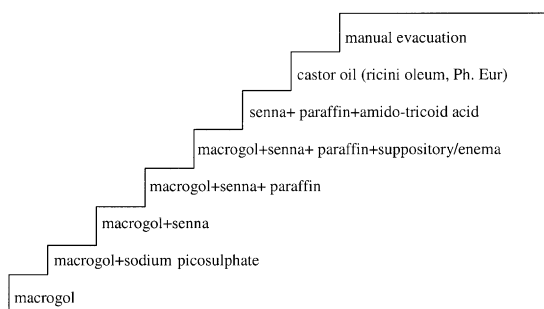
Moreover, in order to achieve satisfying symptom control, the treatment of most of these patients requires relatively large amounts of drugs with constipatory side effects. Nevertheless, physicians must reconsider on a regular basis whether the application of constipation-causing substances may be terminated, although in most cases this is not possible. Physicians would not normally terminate opioid treatment for the management of severe pain, but would start an adjuvant therapy with laxatives.

Any decision to start a pharmacological therapy of constipation must be based on the following pre-conditions:

- A causal therapy of the patient's disease is no longer possible
- A causal therapy of the symptoms caused by this disease is also no longer possible
- The goal of treatment is symptom control
- The treatment of the patient's symptoms requires a great variety and number of drugs
- The physician must be aware of the profile and the adequate treatment of side effects of these drugs.

## Conclusion

Achievement of the best possible palliation of symptoms in palliative care patients frequently requires the use of drugs with a high profile of side effects. Symptom control, therefore, must be conducted in tandem with prophylactic or therapeutic treatment with adjuvant substances. Since most drugs used for palliative medical treatment have constipatory side effects, laxatives play a mayor role in the treatment of palliative care patients. Because of the way the diseases of these patients progress, laxative therapy differs greatly from the procedure used in other patient groups. In patients with an advanced tumour disease, for example, an intake of dietary fibre is not only *not* recommended, it may even be dangerous. The intake of dietary fibre may cause a promotion of constipation and result in faecal impaction, or worse, in bowel obstruction.



**Fig. 5** “Laxative ladder” for the treatment of functional constipation in palliative care patients

Stimulants are of great value in the treatment of palliative care patients—above all, senna preparations, sodium picosulphate and bisacodyl suppositories. Because of its drastic purgatory effect, the application of castor oil is only indicated in very special cases, i.e. if the therapy aims at a promotion of the peristaltic movement in the small intestine.

Among the group of osmotic laxatives, salinic laxatives are not important; saccharine alcohols (sorbitol, mannitol, glycerol) are almost exclusively used in the form of suppositories or enemas.

Our personal opinion is that the use of lactulose for the treatment of opioid-induced constipation is significantly overrated. Meteorism and flatulence are very frequent side effects that are very stressful for patients, and many patients also dislike the sweet taste of lactulose syrups.

In contrast to lactulose, macrogol, another osmotic laxative, is not broken down in the colon and remains unchanged during the intestinal passage. It binds a certain, defined amount of water and causes only negligible electrolyte imbalances. Compared with lactulose treatment, macrogol treatment very rarely causes meteorism and flatulence.

Macrogol is the laxative of choice for prophylactic treatment and therapy of opioid-induced constipation, provided that the patient is able to take in the required amount of fluids.

In contrast to general professional opinion, the application of lubricants (liquid paraffins) is a very useful and necessary additional measure in the treatment of palliative care patients.

The application of rectal laxatives is indicated if the therapeutic goal is to trigger the defecation reflex in order to evacuate soft or hardened bowel contents from a filled rectum. If the aim is also to shorten the duration of the colon passage, the combination with an orally applied laxative is recommended.

The information and clinical experiences discussed above have led to the development of a laxative ladder. This regimen for the treatment of constipation is easy to apply and has proven successful in palliative care (see Fig. 5), and it adds much to the patient's quality of life.

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