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CORE TRAINING FOR DOCTORS

Laxatives: a rational approach to prescribing

Introduction

Constipation is a common clinical presentation – either as a primary complaint, especially in the elderly, or as an incidental symptom. It can cause considerable distress and significantly impact on quality of life. Recognition of constipation is not straightforward as patients vary widely in their threshold for reporting concern about changes in bowel habit. Before laxatives are prescribed, assessment is needed both to exclude important underlying diagnoses such as obstructive lesions, faecal impaction, and metabolic or neurological disorders, and also to confirm that significant constipation is actually present. Management can be difficult, and the choice of laxative prescribed often varies arbitrarily. Laxatives are often selected on a 'trial and error' basis, or prescribed in accordance with personal preference or familiarity with a particular drug, rather than on the basis of evidence.

This article reviews the evidence base for specific laxatives and provides an easy-to-follow rationale for laxative prescribing on the acute medical take. Other measures that may also be required in the management of constipation include enemas, suppositories and biofeedback but further discussion of these is beyond the remit of this article.

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Definition of constipation

The reported prevalence of constipation varies greatly, from 2–27% of the population in western countries (Ford and Suares, 2011), probably largely as a result of variations in the definition of constipation.

For the purpose of clinical trials constipation is defined according to the Rome III criteria (*Table 1*). This is a useful guide for clinical practice but not all patients with symptoms needing treatment will necessarily meet this definition. Some patients may just need reassurance that their defecation rate is within normal limits – between 3 times per day and 3 times per week – and that no laxatives may be needed if stools are soft.

Causes

Constipation is often multifactorial and treatment should never be initiated without considering the cause (*Table 2*). It is particularly important to exclude possible drug-related constipation. 'Red flags' indicating potentially serious underlying pathology and a need for further investigation include iron deficiency, rectal bleeding, recent change in bowel habit in a patient >50 years, weight loss (more than 5%) and a family history of colon cancer.

Table 1. Rome III criteria for definition of functional constipation

Two or more of the following over the last 3 months with symptom onset at least 6 months before diagnosis:	Fewer than three bowel movements per week
	Hard or lumpy stools in at least 25% of bowel movements
	A sense of incomplete evacuation in at least 25% of bowel movements
	A sense of anorectal obstruction or blockage in at least 25% of bowel movements
	Excessive straining in at least 25% of bowel movements
	A need for digital manipulation or support of the pelvic floor to facilitate at least 25% of evacuations
And	Loose stools are rarely present without the use of laxatives
And	There are insufficient criteria for diagnosis of irritable bowel syndrome

From Longstreth et al (2006)

Table 2. Causes of constipation

Dietary and lifestyle	Dehydration or reduced fluid intake
	Anorexia
	Low fibre intake
	Reduced mobility
Motility disorders	Irritable bowel syndrome
	Pseudo-obstruction
	Slow transit
Electrolyte disturbances	Hypokalaemia
	Hypercalcaemia
	Hypermagnesemia
Neurological causes	Dementia
	Multiple sclerosis
	Spinal cord lesions
	Parkinson's disease
	Autonomic neuropathy
Endocrine disorders	Hypothyroidism
	Diabetes mellitus
	Chronic renal failure
Drugs	Opiates
	Anticholinergics
	Calcium-channel blockers
	Calcium-containing agents (antacids, supplements)
	Iron supplements
	Antidepressants (particularly tricyclics)
	Parkinson's medications (particularly anticholinergics)
	Antipsychotics (particularly phenothiazines and clozapine)
Psychiatric causes	Altered attitudes to bowel habits
	Depression
	History of abuse
Late pregnancy	
Structural pathology	Colorectal tumours
	Anal fissure
	Strictures
	Proctitis (proximal constipation)
	Amyloidosis
	Scleroderma
Defecatory disorders	Rectocele
	Solitary rectal ulcer/mucosal prolapse
	Intussusception
	Pelvic organ prolapse

Treatment

The initial approach to constipation should include detection and treatment of any reversible underlying causes, e.g. correction of hypercalcaemia and/or hypothyroidism, as well as addressing lifestyle factors such as fluid and fibre intake and exercise, including encouraging mobilization of hospitalized patients. However, evidence of the effectiveness of these lifestyle measures is limited (Yang et al, 2012) and most cases of chronic constipation will have multifactorial causes, and will need laxative therapy.

Laxatives

Fibre and other bulk-forming agents

Meta-analysis of controlled trials of fibre supplementation with bran or glucomannan shows that it increases the frequency of bowel movements compared to placebo but has no improvement in painful defaecation or use of laxatives (Yang et al, 2012).

Psyllium (ispaghula) from the husk of *Plantago ovata*, typically 3.6 g orally three times/day, improves frequency of bowel movements *vs* placebo and has no significant side effects so merits trial in mild constipation; one study suggested that it may be superior to lactulose, docusate, bisacodyl or senna (Ramkumar and Rao, 2005)(*Table 3*).

Stimulants

Most of the studies of stimulant laxatives are older, sub-optimal trials so evidence of efficacy is often weak but they are still very much in use in clinical practice, and many patients and clinicians find them beneficial (Pare et al, 2007). Senna and bisacodyl are the most commonly prescribed stimulants and work by targeting the myenteric plexus of the colon, stimulating peristalsis.

A double-blinded randomized, placebo-controlled trial showed that bisacodyl is superior to placebo and another randomized study showed comparable benefits with sodium picosulphate (Leung et al, 2011).

There is weaker evidence for the efficacy of senna, with no well-designed randomized controlled trial comparing it with placebo, despite its widespread use (Leung, 2011). However, a randomized controlled crossover study of 77 adult patients with constipation found that a senna–fibre combination was significantly more effective than lactulose, with no change in adverse effects and at a cheaper cost (Passmore et al, 1993).

Side effects of stimulant laxatives can include melanosis coli, abdominal discomfort, cramping and occasionally electrolyte disturbance (Siegel and Di Palma, 2005). Stimulant laxatives have been blamed for causing a 'cathartic colon', but evidence for this is weak, and it is now thought that reported cases more likely reflected a primary motility disorder than a drug effect (Portalatin and Winstead, 2012).

Osmotic laxatives

Osmotic laxatives contain substances that are poorly absorbed, exerting an osmotic effect drawing water into the bowel. Commonly used osmotic laxatives include lactulose, polyethylene glycol (PEG) (e.g. Movicol), glycerin suppositories and sorbitol. Of these, lactulose and PEG have been studied the most.

Lactulose is a non-absorbed disaccharide that is a well-established laxative; many studies are now over 30 years old. The recommended adult dose of lactulose is 15–30 ml once or twice daily and onset of action is 24–72 hours (Portalatin and Winstead, 2012). A meta-analysis by Ramkumar and Rao (2005) summarized results of three double-blinded placebo-controlled trials between 1968 and 1981. In all trials, lactulose significantly improved stool frequency and was generally well tolerated with adverse effects all being predictable consequences of the pharmacology of the drug (lack of absorption leading to fermentation by intestinal bacteria producing flatulence). It is also effective in opiate-induced constipation (Pare et al, 2007).

PEG appears to have greater efficacy than lactulose – a Cochrane review of 10 trials between 1997 and 2007 (686 patients) found that stool frequency increased with PEG by a mean of 0.65 stools per week more than lactulose (95% confidence interval 0.15–1.15) with better stool form (mean improvement of 0.89 units on Bristol Stool chart) (Lee-Robichaud et al, 2010).

This suggests that clinicians should generally prescribe PEG in preference to lactulose, especially given the known flatulent and bloating effects of lactulose. This could be especially important in patients with constipation-predominant irritable bowel syndrome who already tend to suffer with bloating – although there are not yet any controlled trials of PEG *vs* lactulose in these patients (Pare et al, 2007).

Lederle et al (2007) compared sorbitol with lactulose, finding that they had similar efficacy, but lactulose caused more nausea.

Stool softeners

Docusate is very commonly prescribed as a laxative, but is not effective in constipation (Ford and Talley, 2012). Ramkumar and Rao's (2005) systematic review found four studies on docusate, with psyllium being superior to sodium docusate and with no effect of docusate over placebo – concluding that its effects on constipation are 'modest at best'.

Pro-motility agents

One of the most significant recent advances in constipation therapy has been the development of safe agonists of the 5-hydroxy-tryptamine (serotonin) receptor 4 (5-HT_4). Prucalopride is licenced in Europe and Canada for the treatment of constipation in women that is not responsive to conventional therapies. Unlike less selective 5HT agonists it has not been shown to lengthen QT interval and induce arrhythmias (Liu, 2011). Starting dose is 2 mg orally once daily or 1 mg once daily if over 65 years old.

Pro-secretory agents

Lubiprostone is a fatty acid derived from prostaglandin E1 that activates chloride channels and initiates secretion from the intestinal epithelium. It is licenced for treatment of constipation-predominant irritable bowel syndrome. Nausea is a side effect in 24–32% of patients (Gras-Miralles and Cremonini, 2013). Review of three controlled trials shows superiority over placebo (number needed to treat 4; 95% confidence interval 3–7) (Ford and Suares, 2011).

Another new therapeutic class is the guanylate cyclase 2c agonists, represented by

Table 3. Evidence from clinical trials for relative efficacy of different laxatives

Intervention	Reference	Patients	Comparator	Primary outcome	Efficacy	Adverse events
Lactulose	Ramkumar and Rao (2005)	24	Placebo	Stool frequency	4.6 stools/wk lactulose *vs* 1.6 stools/wk placebo	Flatulence, generally well tolerated
		103	Placebo	'Success rate' *	86% success rate compared to 60% placebo	
		47 (meta-analysis)	Placebo	Stool frequency	Lactulose superior to placebo – mean bowel movement/day 0.7 *vs* 0.5 ($P<0.02$)	
Polyethylene glycol (PEG)	Cochrane (Lee-Robichaud et al, 2010)	868 (meta-analysis)	Lactulose	Stool frequency	Stool frequency increased by mean 0.65/week (95% CI 0.15–1.15) for PEG more than lactulose	Nausea, flatulence, diarrhoea (Brandt et al, 2007)
				Form of stool	Stool form better in PEG than lactulose (mean improvement of 0.89 units on Bristol Stool Chart)	
Ispaghula	Ramkumar and Rao (2005)	201	Placebo	Stool frequency	Stool frequency increased from 2.3/wk baseline to 7/wk ispaghula and 4.5/wk placebo	No significant adverse effects
		381 (meta-analysis)	Other laxatives†	Stool frequency and consistency	Ispaghula superior to other laxatives in stool frequency, consistency and acceptability	
Docusate	Ramkumar and Rao (2005)	265 (meta-analysis)	Psyllium	Total stool output	359.9 g/wk with psyllium *vs* docusate 271.9 g/wk ($P=0.005$)	None stated
			Placebo	Stool frequency and consistency	No significant differences between docusate and placebo	
Senna	Agra et al (1998)	91 (opioid constipation)	Lactulose	Defecation-free intervals, general health status	No difference found between lactulose or senna ($P=0.85$)	9.8% vomiting, diarrhoea or cramps
Bisacodyl	Kienzle-Horn et al (2006)	55	Placebo	Stool frequency and consistency	1.8 stools/day compared to 0.95 placebo ($P=0.0061$), improved consistency score ($P<0.0001$)	Similar to placebo
Lubiprostone	Ford and Suares (2011)	610 (meta-analysis)	Placebo	Failure of response	Failed response in 45.1% lubiprostone, 66.9% placebo, relative risk in favour of lubiprostone 0.67 (95% confidence interval 0.56–0.80)	Nausea 24–32%
Linaclotide	Videlock et al (2013)	1604 (irritable bowel syndrome (constipation-predominant))	Placebo	FDA – increased by more than one bowel movement for ≥ 50% of weeks and improvement of ≥ 30% in average abdominal pain	Relative risk favouring linaclotide 1.95 (95% confidence interval 1.30–2.94)	Diarrhoea
		978 (chronic constipation) (meta-analysis)	Placebo	Three or more bowel movements/week and increase of one or more bowel movements/week	Relative risk favouring linaclotide (145 ug/day) 3.80 (95% confidence interval 2.02–6.55)	
Prucalopride	Emmanuel et al (2014)	280 with chronic constipation (meta-analysis)	Placebo	Colon transit time	Colon transit time reduced by 12h (95% confidence interval 19–5h) (2 mg/d) and 14 h (4 mg/d) Increased 0.5 h (-5 to +5) by placebo	Headache, nausea and diarrhoea

FDA = Food and Drug Administration. * Criteria for 'effectiveness' in this trial was the need for any additional laxatives during the treatment period. Considered to be a 'success' if the patient needed ≤1 additional laxatives in 21 days. † lactulose, bisacodyl, docusate, senna, magnesium sulphate

linaclotide as first in class. This has shown good efficacy and is currently licenced for use in patients with moderate or severe constipation-predominant irritable bowel syndrome that has not responded to other treatments (Videlock et al, 2013).

Opioid antagonists

Another significant advance has been the development of opioid antagonists that act selectively on peripheral opioid receptors. Methylnaltraxone is an opioid antagonist that does not cross the blood–brain barrier. It is licenced for the treatment of opioid-induced constipation that is not responsive to conventional laxatives, and has good efficacy for this indication (Ford et al, 2013). Usual dosage is 12 mg once daily by subcutaneous injection (8 mg once/day if <62 kg weight). Alvimopan, which has a peripherally-selective action based on its pharmacokinetics rather than lack of blood–brain barrier passage, is approved for short-term use in the prevention of postoperative ileus. It may also have a role in the management of opioid-induced constipation (Portalatin and Winstead, 2012).

Laxatives in specific situations

Pregnancy and breastfeeding

Constipation in pregnancy should initially be managed by encouragement of increased dietary fibre intake, increased fluid intake and exercise. Bulk laxatives, such as ispaghula, are probably the safest laxative choice in pregnancy should simple measures fail (Wald, 2003). Other laxatives including PEG, sorbitol, lactulose and glycerin suppositories are probably also safe and effective (Portalatin and Winstead, 2012). In large doses, senna will enter breast milk and can cause diarrhoea and colic in infants (World Gastroenterology Organisation, 2007).

Diabetes

Patients with diabetes should generally avoid osmotic sugar alcohols and disaccharides such as sorbitol and lactulose, as their metabolites may cause erratic blood glucose levels.

Irritable bowel syndrome

Given the recognized symptoms of bloating, flatulence and abdominal discomfort in irritable bowel syndrome, patients with irritable bowel syndrome (constipation predominant) should avoid lactulose or sorbitol, which can produce similar adverse effects and may therefore exacerbate symptoms. Randomized placebo-controlled trials of lactulose have not been conducted in this patient group. In a recent multi-centre, randomized, double blinded placebo-controlled trial, linaclotide improved all of five specified abdominal symptoms in irritable bowel syndrome (constipation predominant) (fullness, bloating, discomfort, pain and cramping), with noted improvements in quality of life scores ($P<0.01$) compared with placebo (Rao et al, 2014).

Opioid-induced constipation

There are few high quality trials in this area but stimulant and osmotic laxatives are still the mainstay of treatment. Stimulant laxatives, such as senna, are usually the preferred initial choice (Twycross et al, 2012). PEG is preferred to lactulose, because of the bloating and/or flatulent effect often seen with lactulose. In terminally ill patients fibre or bulking agents are best avoided as they usually require an increased volume of fluid intake that may not be feasible. Methylnaltrexone is effective in relieving opioid-induced constipation (Clemens et al, 2013) and should be used if simpler measures have failed.

Putting it into practice

After having excluded faecal impaction (often requiring manual evacuation or enemas), reversible causes and red flags, the first treatment for mild constipation should usually be fibre or bulk-forming agents such as isphagula. Should this fail, an osmotic laxative should be trialled next, with PEG preferred to lactulose. If the constipation is secondary to opioids that cannot be ceased, then stimulant laxatives should be considered first.

If there is no success with the above measures, the doses should be titrated up. Although it is often recommended to 'add in' a stimulant laxative after initially trialling an osmotic laxative (Leung et al, 2011), there is a surprising lack of trials comparing two or more agents with one. If there is still no success, then specialist advice should be sought and newer agents should be considered, e.g. linaclotide, prucalopride, lubiprostone and methylnaltraxone. Of these newer agents, linaclotide should be considered for patients with irritable bowel syndrome (constipation predominant), and methylnaltraxone for opioid-induced constipation.

Figure 1 shows an algorithm for an appropriate sequence of treatments for constipation.

Conclusions

Constipation is a common, debilitating condition that requires management to be tailored to the individual. There has been a gradual shift from stimulant laxatives towards osmotic laxatives, with PEG better tolerated than lactulose. Considerable progress is now being made in the development of new agents that may be particularly effective in opioid-induced constipation. It is surprising that for such a common condition, there is a lack of good quality evidence surrounding the efficacy of commonly used treatment options such as stool softeners and lifestyle advice. There is also a need for good quality trials comparing 'add-on therapies' *vs* single drugs. **BJHM**

Conflict of interest: none.

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TOP TIPS

- Remember to screen for 'red flags' and look for any underlying reversible cause, e.g. constipating drugs or electrolyte disturbance.
- If faecal impaction is present on rectal examination, enemas or manual evacuation are needed before giving laxatives.
- Opt for polyethylene glycol as first-line osmotic laxative.
- Consider using methylnaltrexone for opioid-induced constipation if no success with osmotic or stimulant laxatives.
- Avoid lactulose or sorbitol in diabetic patients, or patients with irritable bowel syndrome (constipation predominant).
- Avoid bulking agents in palliative care patients as they may struggle to take in the required fluid for these to work.

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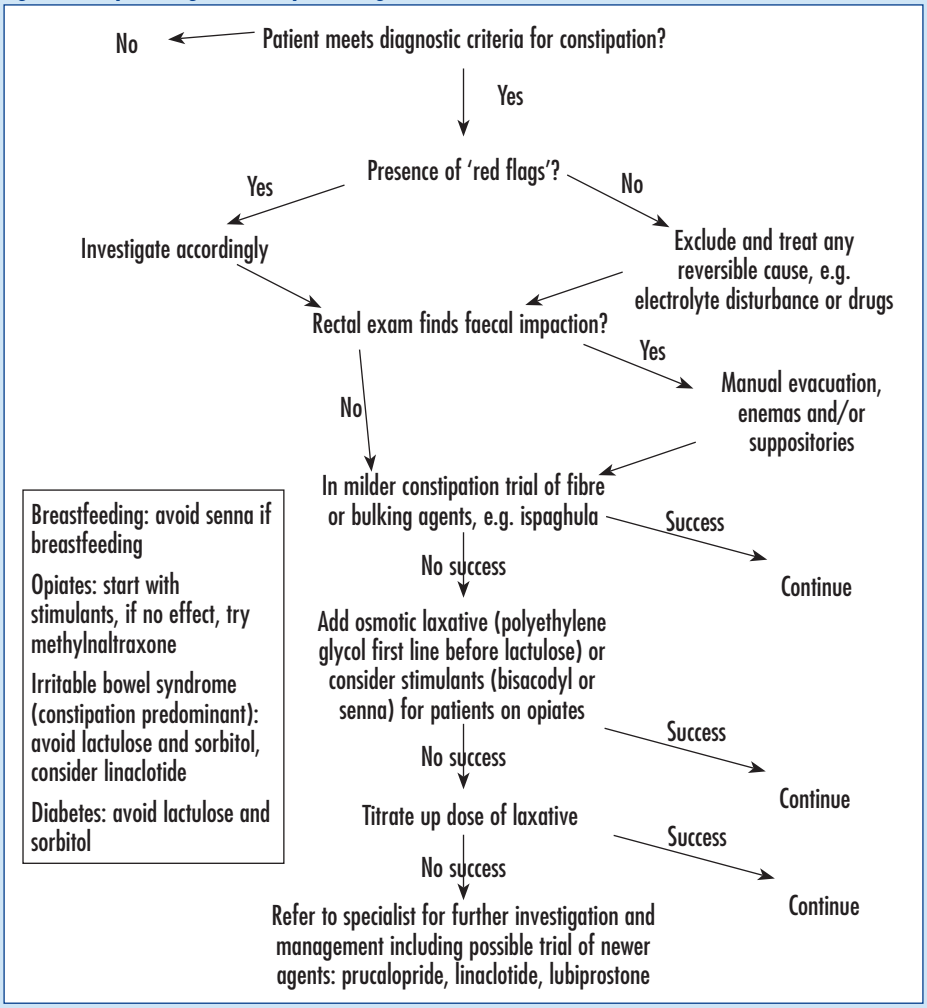
Figure 1. Proposed algorithm for prescribing laxatives.



KEY POINTS

- Psyllium (ispaghula) has proven efficacy and no significant side effects.
- There is little evidence to support the use of sodium docusate in the management of constipation, despite its widespread use.
- Evidence to support the use of stimulant laxatives such as bisacodyl and senna is weak, although there is modest evidence to support their use in opioid-induced-constipation.
- Polyethylene glycol (Movicol) has greater efficacy than lactulose.
- Lactulose may increase bloating and should be avoided in patients with irritable bowel syndrome (constipation predominant).
- Stool softeners such as docusate have no proven efficacy in constipation.
- Linaclotide is effective in patients with irritable bowel syndrome (constipation predominant) who are not responding to other laxatives.

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