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Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

Effectiveness of laxatives in adults

This bulletin summarises the research evidence on the effectiveness of laxatives in the treatment of constipation in adults.

- Laxative treatments are associated with increases in bowel movement frequency and improvements in the symptoms of constipation
- Bulk (fibre-based) laxatives and osmotic laxatives are associated with increases in frequency, and improvements in stool consistency and symptoms
- Little evidence is available as to the comparative effectiveness of bulk and non-bulk laxatives in the treatment of constipation
- There is no good evidence that laxatives prevent constipation in older patients
- A stepped approach to laxative treatment would seem justified, involving initial treatment with cheaper laxatives, before proceeding to the more expensive alternatives
- There is a need for large comparative trials of different strategies for the management of constipation in adults including comparisons of the effectiveness of different classes of laxatives.

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A. Background

Constipation is a common reason for GP consultations in adults. The UK National Survey of Morbidity in General Practice in England and Wales found consultations for constipation were particularly common among the very young and the very old.[1] The prevalence is less than 10% in the UK general population,[2] about 20% among older people living in the community,[3] and higher still among those living in nursing homes.[4] About half of all patients admitted to specialist palliative care units report constipation, but about 75% will require laxatives.[5] Laxatives are required by 87% of terminally ill patients taking strong oral opioids, 74% of those on weak opioids and 64% of those not receiving opioid analgesia.[6] There also appear to be socio-economic, gender, regional and national differences in the prevalence of constipation.[3,7] Constipation adversely affects the quality of life of the sufferer[8] and accounts for a significant proportion of the NHS drug bill.[9] At over £46 million per year in England, expenditure on the four main types of laxative (bulk, osmotic, stimulant and softener) is higher than on hypnotics and anxiolytics (e.g. benzodiazepines).[10]

A.1 Defining constipation

A frequency of defecation of less than three times a week has been widely used as an objective criterion for defining constipation,[11,12] though patients' definitions emphasise symptoms such as pain and straining rather than frequency.[13] The 'Rome II' diagnostic criteria for constipation, which tend to be used as inclusion criteria for laxative trials, require two or more criteria to be present for at least 12 weeks in the last 12 months in the absence of a structural or biochemical explanation (Box 1).[14]

A.2 Risk factors for constipation

Diet

The prevalence of constipation may be increasing because modern food processing methods have produced a refined roughage-free diet.[15,16] Dietary fibre intake is positively associated with increases in bowel movement frequency and faecal mass and reductions in bowel transit time and symptoms. (For overviews see Spiller, 1994[17]; Bennett & Cerda 1996.[18]) Studies also show a lower incidence of constipation in vegetarians.[19,20] One large population survey carried out in the USA has found that constipated adults report lower consumption of beans, peas, fruit and vegetables.[21] Frequency of consumption of fruit, vegetables and bread declines significantly with age in UK adults.[22] Low calorie intake in older people, (adjusted for fibre consumption), has also been implicated in the aetiology of constipation.[23]

A meta-analysis of the effects of wheat bran which incorporated twenty comparative studies (non-randomised controlled trials) of the association between stool weight and gastrointestinal transit time found that bran supplementation resulted in increased stool weight and decreased transit time in both healthy and constipated adults.[24] However, in constipated patients receiving bran, stool weight remained lower than in controls, suggesting that low dietary fibre intake may not be the only factor influencing constipation.

Box 1 Rome II Criteria for functional constipation, updated 1999 [14]

1. Straining at defecation at least a quarter of the time;
2. Lumpy and/or hard stools at least a quarter of the time;
3. Sensation of incomplete evacuation at least a quarter of the time;
4. Three or fewer bowel movements per week.

Two or more of the above should be present for at least 12 weeks out of the preceding 12 months

Fluid intake

Low fluid intake has also been cited as a risk factor for constipation.[25,26] Older people in particular may be at risk as they may drink less in an attempt to control incontinence.[25] There have been few studies that have examined the effects of low fluid intake on constipation while controlling adequately for other factors. However, studies have shown low fluid intake to be related to slow colonic transit[23] and low stool output in healthy adults.[27] A large USA survey also reported lower consumption of beverages (sweetened, carbonated and non-carbonated) in constipated adults.[21] A community survey in New Zealand, however, found no association between reduced fluid intake and constipation.[28]

No trials have systematically assessed the impact of fluid intake as a treatment, though one small trial has included 400ml/day of water as a control intervention, and found it to be less effective than fibre plus the same amount of water.[29] The authors of another small laxative trial also suggested that the dose-response effect which they observed may have been partly due to the associated increased intake of fluid.[30] However the effectiveness of increased fluid intake as a treatment for constipation remains largely unknown at present.

Mobility

Constipation has been found to be more prevalent in those who take little exercise or are relatively inactive,[21] and this association persists after controlling for age. The highest risks are associated with being chairbound or bedbound.[31] Several studies have described bowel management programmes in institutionalised patients which have recommended exercise in the treatment of constipation.[32,33] Other studies have also recommended exercise[13,34] on the basis that there is an association between physical inactivity and the prevalence of constipation in older people.[3]

However these interventions appear not to have been formally evaluated in constipated patients.[35]

Drug treatments

Use of drugs that can cause constipation is also important, in particular anticholinergic anti-depressants, opioid analgesics and NSAIDs including aspirin.[36-38]

Other risk factors

Other factors which have been implicated in the development of constipation include anxiety, depression and impaired cognitive function. For a more extensive list of risk factors associated with constipation see the 1997 NHS HTA review.[3] The validity of many suspected risk factors for constipation has been questioned by some researchers as they have not been systematically investigated.[39]

A.3 Treatment of constipation

A number of different interventions have been used in the treatment of constipation. Non-pharmacological interventions include guar gum, bread, bran, lentils, aloe vera, and fruit. Some of these treatments may act by increasing dietary fibre, while others have a stimulant action. Aloe is a folk remedy, which like senna and rhubarb contains anthraquinone derivatives with a stimulant effect. Fruit may work by increasing bulk and liquid in the diet, and/or by fermentation in the colon. Other non-pharmacological treatments for constipation include abdominal massage, biofeedback, hypnosis and yogic breathing. None of these interventions are evaluated in this bulletin.

Box 2 Main categories of laxatives

Bulking agents (eg bran, ispaghula) which increase the amount of fibre in the diet, increasing the weight and water-absorbent properties of the stool.

Stimulant laxatives (eg senna, bisacodyl) which increase intestinal motility by stimulation of colonic nerves.

Faecal softeners such as liquid paraffin soften the stool. It has been recommended that the use of these faecal softeners should be discouraged altogether on the grounds of their adverse effects including anal seepage and irritation.[40]

Osmotic laxatives (such as magnesium hydroxide, lactulose) also act by softening and increasing water absorption in the stool. The most commonly used of these in Britain is lactulose, which may also have some stimulant effect. Lactitol is a similar agent and may also work by improving stool characteristics through encouraging the fermentation of anaerobic bacteria.

Table 1 Systematic reviews of effectiveness of laxatives in adult patients

Author (year)	Inclusion criteria	Main results
NHS HTA review (1997)[3]	RCTs in any language were included if all participants were 55 years or older, and were treated for chronic constipation with any oral laxative	Laxatives improve bowel movement frequency, consistency and symptoms in older adults. There is little evidence of differences in effectiveness between laxatives, and no good research evidence to support current NHS trends towards prescribing the more expensive stimulant laxatives
Tramonte et al. (1997)[43]	English language RCTs of laxative or fibre therapies in constipated adults (all ages)	Laxatives and fibre increased frequency by overall weighted average of 1.4 (95% CI: 1.1-1.8) bowel movements per week, and decreased abdominal pain and improved consistency. No clear evidence found as to superiority of various treatments

Laxatives are the most commonly prescribed pharmacological interventions, of which there are four main types (see Box 2). Prescribing of bulk-forming laxatives is decreasing yearly, while that of stimulant and osmotic laxatives is increasing.[10]

A.4 Who should be treated with laxatives?

In general, there is much uncertainty over what constitutes effective management of constipation and laxatives may not be appropriate in all constipated patients. For mobile people (including older patients), it has been suggested that lifestyle changes involving changes in diet, increasing fluid intake and increasing physical activity may be sufficient,[41] though treatment will ultimately depend on the underlying causes and severity of the constipation. It has also been suggested that mild constipation can be managed with increasing fibre in the diet, whilst more severe constipation may require treatment with pharmacological laxatives, after exclusion of underlying pathology.[42] Only a small minority with intractable constipation will require referral for further investigations.[41]

B. Nature of the evidence

This bulletin is based largely on two systematic reviews[3,43] (Table 1) and on the additional randomised controlled trials (RCTs) identified since the publication (1997) of these reviews (Tables 2 and 3). (See appendix for further details of review methods.) The first of these reviews was commissioned by the NHS HTA programme and was published in 1997.[3] This review included 10 RCTs (involving 367 participants) that had evaluated the effectiveness of laxatives used in older patients with constipation. The second systematic review included adults of any age and again focused on the effectiveness of laxatives.[43] Only RCTs which involved patients with a minimum duration of constipation of two weeks, evaluated treatment for at least one week and assessed clinical outcomes such as bowel movement frequency, consistency or symptoms were included. Thirty-six trials were identified for inclusion in this review, involving 1815 participants of which 70% were women, in a variety of settings including clinics, hospitals and nursing homes.

Because the definitions of constipation adopted by the original systematic reviews exclude underlying pathology, the use of laxatives in the treatment of terminally ill patients is not covered in this bulletin.

One other recently published systematic review was identified which included RCTs of docusate for constipation in chronically ill patients.[44] All studies showed a trend in favour of increased bowel movement frequency with docusate. However, it was concluded that treatment of constipation in chronically ill patients is based on inadequate experimental evidence.

C. Effectiveness of laxative treatments

C.1 Bulk laxatives

The average weighted mean increase in bowel frequency associated with treatment with bulk laxatives is around 1.4 bowel movements per week in adults.[43] The increase associated with treatment with other laxative agents is approximately 1.5 bowel movements per week, with no significant differences between bulk and non-bulk laxatives.[43] Four additional RCTs carried out in populations of ambulant and institutionalised patients that were identified for this bulletin (Table 2) suggest an increase in frequency of up to 1 bowel movement per week with bulk laxatives compared to placebo. However these trials are very small, and/or have methodological problems.[29,45-47]

A double-blinded comparative study involving bulk laxatives found a significantly greater increase in frequency and feelings of complete evacuation with fibre compared to docusate sodium.[48] Overall, the evidence from these new RCTs and previous systematic reviews suggests that bulk laxatives are associated with an increase in frequency of 1-2 bowel movements per week compared to placebo and may be better tolerated than other laxative products.

Most trials that have evaluated fibre or bulk laxatives have found an improvement in abdominal pain with treatment, though no comparisons were significant.[43] Consistency of the stool was improved in laxatives compared to placebo. A recent unblinded RCT compared ispaghula (Fybogel®) with lactulose in 473 patients recruited by 65 GPs in the UK. This study found that ispaghula was more effective overall than lactulose, with greater tolerability and fewer adverse effects, though frequency data are not reported.[49]

There is little comparative evidence that there are differences between bulk and other laxatives in terms of frequency or symptoms.

C.2 Stimulant laxatives

No consistent evidence was found that stimulant laxatives are more effective than non-stimulant laxatives. In trials conducted among older adults (>55 years) there is also little evidence of differences in effectiveness between categories of laxatives, and no trial evidence to suggest that the more expensive stimulant dantron (danthron) based laxatives are more effective than cheaper alternatives.[3] (Note: the BNF now states that dantron should only be prescribed for constipation in terminally ill patients.)[50]
A combination of a bulk plus stimulant laxative (Agiolax® – available as Manevac® in the UK) has been reported in two good quality trials of older adults to be more effective in improving consistency and frequency than an osmotic laxative (lactulose).[3]

C.3 Osmotic laxatives

Laxatives with an osmotic effect appear to be consistently associated with significant improvements in frequency, consistency, straining and pain compared to placebo, based on the results of the two systematic reviews[3,43] and the additional small trials identified for this bulletin. [51-54]

There is little evidence for differences in effectiveness between osmotic laxatives and other treatments. Two small hospital-based RCTs compared polyethylene glycol '3350' (PEG '3350') with lactulose[55] and Konsyl® (ispaghula)[56] respectively. Both trials suggest that PEG '3350' may produce a greater increase in frequency than either comparators, with no significant difference in the incidence of adverse effects. In addition the use of PEG '3350' may result in a greater reduction in straining than lactulose.[55] Another small trial has reported lactitol and lactulose to be equally effective.[57]

C.4 Other classes of laxatives

Laxatives with a softening action appear to be more effective than placebo in terms of increasing frequency and overall symptom improvement,[3,43] but again there is little evidence available as to their comparative effectiveness. One additional trial was identified which supports this conclusion.[58] A crossover trial combined a softener with a stimulant and found that this was associated with an increase in frequency compared to placebo.[59] Both these trials are very small.

D. Adverse effects and quality of life

Few studies have used standardised outcome measures to assess adverse effects and/or quality of life, though most studies did not report an increase in pain with fibre or non-bulk laxatives. Only two trials have examined improvements in general well-being, neither of which showed any difference between fibre and

Table 2 Additional trials evaluating single laxative treatments in adults

Author (Country,Year)	Population	Intervention	Results	Comments Funding Details
Parallel RCTs				
Ashraf et al (USA, 1995)[45]	Ambulant patients Mean age: 51 yrs 64% female	*Bulk vs placebo* I: Metamucil (n=11) 5g/day C: Placebo (n=11) 8 weeks	*Frequency*: I: increase in BM/week from 2.9 (0.1) to 3.8 (0.4) (p<0.05). C: No data given, estimated from graph: 2.7 vs 2.9 *Pain score (range 1-7)*: I: Decreased from 2.6 (0.5) to 2.0 (0.4), p<0.05. C: Slight increase (from Fig 3c): 2.7 vs 2.8 No significant group differences in consistency, straining, evacuation, or side effects.	Quality score: 3 Randomisation: stated Double blind Description of dropouts Funding: Proctor and Gamble
Howard et al (USA, 2000)[46]	Institutionalised men from a single care centre Mean age intervention: 73 yrs Mean age comparator: 74 yrs	*Bulk vs usual care* I: Bran mixture: (n=6) 3 cups apple sauce, 2 cups coarse wheat bran, 1.5 cups prune juice C: Usual care (n=6) normal diet, laxatives and enemas as needed 4 months	*Frequency* (BM/week): End of treatment: I=2.3 (0.39), C=2.7 (0.79), (ns) *Number of bowel medications*/week: End of treatment: I=1.39 (1.08), C=13.28 (5.68) (p=0.03). Reduction of bowel medication with bran at maximum dose (p=0.03)	Quality score: 1 Randomisation: not stated Open study Funding: not stated
Sculatti & Giampiccoli (Italy, 1984)[29]	Ambulant patients Mean age: 67.4 yrs 83% female	*Bulk vs water* I: Fibraform (n=20) 7g/day+400ml water C: Water (n=20) 400ml 30 days	*Overall effectiveness*: % non-constipated at 15 days: I=30%, C=5% p=0.09. At 30 days: I=74%, C=15% p=0.001. *Consistency*: % with soft faeces at 15 days: I=25%, C=20% p=0.9. At 30 days:I=84%, C=25% p=0.0001 *Painful defecation*: % Pain-free at 15 days: I=73%, C=64% p=0.5. At 30 days: I=90%, C=67% p=0.13.	Quality score: 2 Randomisation: not stated Not blind Description of dropouts Funding: not stated
Corazziari et al (Italy, 1996)[51]	Outpatients Mean age: 41.8 yrs 77% female	*Osmotic vs placebo* I: PMF-100 (Normopeg) (n=25) 14.6g PEG 4000, 1.42g anhydrous sodium sulphate, 0.42g sodium bicarbonate, 0.18g potassium chloride, 0.01 simethicone, flavoured C: Placebo (flavoured maltodextrine)(n=23) 4 week run-in, then 8 weeks PMF-100 or placebo twice daily in 250 ml of water.	*Frequency* (BM/week): End of 4 week run in: I=2.2 (0.5), C=1.9 (0.8) End of 8 week treatment period: I=4.8 (2.3), C=2.8 (1.6). Bowel frequency normalised: I= 64%, C= 22% (p<0.008; per ITTanalysis p<0.04) *Consistency*: % with hard stools : I=12%, C=50% (per ITT analysis p<0.07) *Use of laxatives*: I=16%, C=48% (p<0.03; per ITT analysis p<0.1) *Straining*: I=8%, C= 41% (p<0.03). No group differences in occurrence or severity of other symptoms.	Quality score: 4 Randomisation: stated Double-blind Description of dropouts ITT Funding: not stated
Corazziari et al (Italy, 2000)[52]	Outpatients Mean age intervention: 42.4 yrs Mean age comparator: 43.2 yrs 82.9% female	*Osmotic vs placebo* I: PMF-100 (Normopeg) (n=33), as in Corazziari (1996) trial, above C: Placebo (flavoured maltodextrine) (n=37) 4 week run-in, then 20 weeks of PMF or placebo as above	*Frequency* (BM/week): Week 4 (end of run-in): I=8.3 (4.0), C=7.7 (4.3). Week 12: I=7.4 (3.1) C=4.3 (2.5). Week 24: I=7.4 (3.2), C=5.4 (2.1) Mean consumption of non-study laxatives, previous 4 weeks: Week 4: I=1.1 (2.8), C=0.31 (0.74). Week 12: I=0.7 (2.7), C=2.2 (3.3). Week 24: I=0.2 (0.8), C=1.4 (2) Mean number of drug sachets, previous 4 weeks: Week 4: I=38 (12) C=38 (15). Week 12: I=33 (13), C=43 (12). Week 24: I=33 (13), C=44 (12) Number of adverse events: I=57, C=41	Quality score: 4 Randomisation: stated Double-blind Description of dropouts Funding: not stated
DiPalma et al (USA, 2000)[53]	Participants recruited from gastroenterology practices and local advertising Mean age intervention: 46.7 yrs Mean age comparator: 45.8 yrs Overall mean age: 45 yrs 87% female	*Osmotic vs placebo* I: Braintree PEG 3350 (Miralax) (n=80). 17g/day in approx 8 oz water or juice C: Dextrose powder placebo (n=71) same size scoop/day as I in 8oz water or juice 14 days	*Frequency* (BM/week): Week 1: I=4.2 (2.8), C=2.9 (1.9). Week 2: I=4.5 (3.0) C=2.7 (1.8) *Treatment success* (>3 BM/week): Weeks 1 and 2 I=72.2%, C=49.6% (p<0.001; p<0.05 on ITT analysis). *Patient-rated effectiveness*: I=68%, C=40% (p<0.001) *Investigator-rated effectiveness*: I=71.4%, C=47.1% (p<0.005) *Other*: Significant improvements in self-reported consistency, straining passage, cramping and flatus (all p=0.001)	Quality score: 3 Randomisation: stated Single blind Description of dropouts ITT Funding: Braintree Laboratories
Huys & Van Vaerenbergh (Belgium, 1975)[58]	Hospital in-patients Mean age: not stated Ratio male:female not stated	*Softener/stimulant vs placebo* I: Softener (n=15) 60mg DSS, 50mg of 1.8-dioxyanthraquinone C: Placebo (n=15) 10 days 'preparation' then 20 days treatment	*Frequency*: % patients with daily stools: I: pre: 32%; post: 72%. C: pre: 33%; post: 47%. Significant group difference, no alpha stated. No difference in diarrhoea incidence	Quality score: 2 Randomisation: not stated Double-blind Description of dropouts Funding: not stated

Table 2 (cont...) Additional trials evaluating single laxative treatments in adults

Author (Country,Year)	Population	Intervention	Results	Comments Funding Details
Crossover RCTs				
Marsicano (Venezuela, 1995)[47]	Hospital cardiology patients Mean age: 40.1 yrs, all female	*Bulk vs placebo* I: Glucomannan fibre. 3g/day and 4g/day C: Placebo (n=60) 5 weeks (2 weeks washout)	*Frequency*: I: 3g: Increase of 0.47 bm/day, compared with 4g: increase of 0.83 bm/day C: Change of - 0.2 to 0.1 *Straining*: 9 cases with placebo (15%), 5 (8.3%) with 3g and 6 (10%) with 4g Glucomannan *Diarrhoea*: I: Glucomannan 3g 6 (10%), 4g: 5 (8.3%), Placebo: 1 (2%). *Flatulence*: Glucomannan 3g: 10 (17%), Glucmannan 4g: 13 (22%), Placebo: 11 (18%)	Quality score: 3 Randomisation: stated Double-blind Description of dropouts Funding: not stated
Andorsky (USA, 1990)[30]	Outpatients Mean age: 62yrs 76% female	*Osmotic vs placebo* I: PEG, 8 or 16 oz daily C: Placebo (N=37) 5 days (2 day washout)	*Frequency* (BM/5 day period): I (8oz)=5.81 (3.92), C=4.36 (2.8) I (16oz): 9.56 (4.41), C=5.38 (2.44). Overall, PEG significantly more effective than placebo, and 2 glasses more effective than 1. *Consistency score (range 1-4)*: PEG significantly more effective than placebo (2.6 vs 1.2; p<0.05), and 2 glasses more effective than 1 (2.7 vs 0.8; p<0.05). *Side effects*: Problems with cramps, gas, nausea, loose stools and taste with PEG but none resulted in termination of trial. 9/37 (24%) had transient gas/cramps.	Quality score: 2 Randomisation: stated Double-blind No ITT Authors note that greater effect of 16oz may be due to fluid intake Funding: drugs donated by Reed and Carnrick Pharmaceuticals
Castillo (Argentina, 1995)[66]	Ambulant patients Mean age: not stated Ratio male:female unclear	*Osmotic vs placebo* I: Lactulose, 30ml/day C: Placebo 4 weeks (2 weeks washout)	*Overall effectiveness*: Number of satisfactory or partially satisfactory treatments at 1 week: I=23, C=17 (p<0.01) at 1 week. I=22, C=8 (p<0.01) at 4 weeks *Adverse effects*: Number of patients with meteorism: I=3, C=6, p not stated. Flatulence: I=5, C=3, p not stated	Quality score: 1 Randomisation: not stated Double blind No ITT analysis Funding: not stated
Lemann et al (France, 1994)[54]	Patients with chronic constipation Mean age: 48 yr 85% female	*Osmotic vs placebo* I: PEG 3350 13-39 g/day C: Placebo (N=32)	*Frequency* (BM/week): I: 9.4 (4.3) C:4.7 (3.4) (p<0.001) *Straining score (range not stated)*: Lower with PEG (0.7 (0.7) vs 1.6 (0.7), p<0.001). *Overall improvement*: Greater with PEG (score 6.4 vs 1.6, P<0.001; score range not stated)	Quality score:2 Randomisation: not stated Double blind No dropouts reported Funding: Norgine Pharma

Table 3 Additional trials comparing laxative treatments in adults

Author (Country,Year)	Population	Intervention	Results	Comments Funding Details
Parallel RCTs				
Attar France & Scotland, 1999)[55]	Recruited from general and geriatric hospitals Mean age: 55 yrs 82% female	*Osmotic vs osmotic* I: PEG 3350 low dose (n=60) Mean=1.6 x 13g sachets/day C: Lactulose (n=55) Mean=2.1 sachets x 10g/day 4 weeks	*Frequency* (BM/day): I=1.3 (0.7), C=0.9 (0.6), p=0.005. Proportion passing <3 BM/week: I=10%, C=14% Straining (Median score; range 0 (absence)-3 (severe)): I=0.5 (0.7), C=1.2 (0.9), p=0.0001 *Overall improvement:* (VAS, range 0 (no change) -10 (excellent)): I=7.4 (2.5), C=5.2 (3.3), p<0.001 *Adverse events:* 2 in PEG group, 1 in lactulose group Use of suppositories/enemas: I=16%, C=34%, p=0.04 Symptoms No difference in % with liquid stools, pain, bloating, flatus, rumbling. More days with flatus with lactulose (I=9.2 (10.1), C=3.8 (6.8)). Mean number of liquid stools higher with PEG (I=2.4 (3.5), C=0.6 (1.2), p=0.001)	Quality score: 2 Randomisation: stated Single blind No ITT analysis Funding not stated
Bobbio (Italy, 1995)[67]	Patients with chronic constipation Mean age: 63.5yrs 63% female	*Osmotic+bulk vs osmotic* I: Lactulose+glucomannan (n=20). 12g/day (24% glucomannan, 70% lactulose) C: Lactulose (n=20). 8.4g/day 4 weeks	*Frequency* (BM/week): I: 5.75 (0.29); C: 6.55 (0.18), p<0.05 *Flatulence*: Mean change in score; range 0 (symptom absent) -2 (intense): I=-0.2, C=+0.7, p<0.01 *Meteorism score*: I=-0.1, C=0.8, p<0.001 *Pain score*: No difference between groups. *Tolerance score (range 0 (low tolerability)-3 (optimum tolerability))*: I=2.2, C=1.9, p<0.05	Quality score: 2 Randomisation: not stated Double blind No dropouts reported Funding not stated
Norgine Ltd unpublished data (China, 2001)[56]	Hospital population Mean age intervention: 51yrs 64% female Mean age comparator: 50 yrs 56% female	*Osmotic vs bulk* I: PEG 3350 plus electrolytes (n=60) 13.7g/bag twice/day C: Konsyl (ispaghula) (n=60) 3.5g/bag twice/day 14 days	*Frequency* (BM/week): Increase in BM at 1 week vs baseline: I=6.95 (3.46), p=0.0001, C=3.98 (2.68), p<0.0001. At 2 weeks vs baseline: I=7.48 (3.54), C=4.33 (2.40), p<0.0001. *Consistency*: % normal stools: Week 1: I:84%, C: 52%, p=0.001. Similar results for 2nd week *Overall efficacy*: I:Overall effectiveness rate = 92.07%, C: 73%, p=0.005 *Adverse events*: I: 12%, C: 8%, p=0.5 (ns)	Quality score: 3 Randomisation: stated Unclear whether blinded Description of dropouts Funding: Norgine Ltd

Table 3 (cont...) Additional trials comparing laxative treatments in adults

Author (Country,Year)	Population	Intervention	Results	Comments Funding Details
Dettmar & Sykes (UK, 1998)[49]	Participants recruited by 65 GPs Mean age: unclear 63.4% female 35.3% male 1.3% not recorded	*Osmotic vs bulk vs other* I: Ispaghula husk (Fybogel) (n=224) 3.5g twice/day with water C1: Lactulose (n=91) C2: Other prescribed laxatives (n=79): (bisacodyl (n=24), softener (n=21), senna (n=18), docusate sodium (n=13), magnesium sulphate (n=3)) 4 weeks	*Overall effectiveness*:Self-reported overall effectiveness (77% excellent or good with ispaghula versus 61% lactulose, 49% other), palatability (62%, 49%, 50%) , acceptability (73%, 49%, 50%), all higher with ispaghula with fewer adverse effects (all p<0.01). *Consistency (% normal)*: 55% vs 43% vs 39% (p<0.05) *Speed of action*: No difference in onset time of first bowel movement. *Other symptoms*: Lower incidence of pain and diarrhoea with ispaghula husk	Quality score: 2 Randomisation: not stated Open study Description of dropouts Funding: Reckitt and Colman
Gordin (France, 1997)[68]	Ambulant patients Mean age: not stated Ratio male:female not stated	*Osmotic+stimulant vs osmotic* I: Lactulose and paraffin (n=36) 15ml/day C: Lactulose 50% (n=36) 15ml/day 2 weeks	*Frequency*: Patients with 1 or 2 BM/day: I=88%, C=81% (ns) *Overall effectiveness*: % patients self-reporting good or very good improvement: I=76%, C=54%, p=0.05 *Tolerability*: % patients reporting good or very good: I=70%, C=40% (p=0.01) *Consistency*: % "Soft" I=61%, C=55%	Quality score: 1 Randomisation: not stated No blinding No ITT analysis Funding not stated
Hammer & Ravelli (Germany, 1992)[57]	Ambulant patients Mean age: 54 yrs 81% female	*Osmotic vs osmotic* I: Lactitol (Importal) (n=31). 20g/day for 3 days, then 10g/day for 25 days (maintenance dose) C: Lactulose (Dulphalac) (n=26). Initial dose 20.1g for 3 days, then 13.4g for 25 days 4 weeks	*Frequency* (BM/week): I=6.7 (4.39) C=7.4 (4.48) % patients with ≥3.5 BM/week at end of study: I=82%, C=81% *Consistency*: % patients reporting 'normal' or 'soft' at end of trial: I=19/25 (76%), C=16/24 (67%) p=0.50 *Overall effectiveness and tolerability*: No significant difference between in I and C in terms of patients', or physicians' ratings *Adverse effects*: % reporting adverse effects: I=10/32 C=16/26 p=0.02	Quality score: 2 Randomisation: not stated Open study Description of dropouts Funding not stated
Heitland & Mauersberger (Germany, 1988)[69]	Participants were laxative users Mean age intervention: male 52 yrs, female 64 yrs Mean age comparator: male 58 yrs, female 65 yrs	*Osmotic vs osmotic* I: Lacitol (Importal) (n=30) mean dose 20g/day as single dose C: Lactulose (Dulphalac) (n=30) mean dose 20g/day as single dose (30ml Dulphalac syrup). 2 weeks	*Frequency* (BM/day): After 2 weeks treatment: I=0.87 C=0.79 (0.05<p<0.1, n.s.). No significant difference in number of patient days with 1 or more bowel movements. No significant differences in consistency, side effects or other symptoms (bloating, flatulence, nausea, cramping, diarrhoea)	Quality score: 0 Quasi-randomised: (alternation) Open study Funding not stated
McRorie (USA, 1998)[48]	Ambulant patients Mean age: 37 yrs 92% female	*Bulk vs stimulant/softener* I: Psyllium (n=88) 5.1g twice/day C: Docusate sodium (n=82) 100mg twice/day 2 weeks	*Frequency* (BM/week): By week 2: I=3.5 (0.22), C=2.87 (0.22), p=0.02 *Consistency*: Score on 7 point scale for each symptom (1=normal, 7=constipated, or extreme symptoms): I=3.1 (0.14), C=3.2 (0.15), p=0.29 *Straining score*: I=2.8 (0.15), C=3.1 (0.16), p=0.15 *Stool water content*: I=74%, C=72%, p=0.004 *Pain score*: I=2.04 (0.13), C=2.3 (0.14), p=0.12 *Evacuation incompleteness score*: I=2.9 (0.15), C=3.2 (0.17), p=0.04	Quality score: 3 Randomisation: stated Double blind ITT analysis Funding: Proctor & Gamble
Crossover RCTs				
Lugli et al (Italy, 1990)[70]	Ambulant patients Age range 26-70yrs 53% female	*Bulk vs bulk* I1: Methyllcellulose (MC), 1g/day I2: Wheat bran (WB), 24g/day I3: Ispaghula (IH), 7g/day (N=30) 7 days (with 1 week washout)	*Frequency* (Mean BM/day): IH and WB higher than MC (P<0.001); actual data not reported. IH vs WB: No difference *Adverse effects*: No adverse events for any preparation and all well tolerated; no data on other symptoms	Quality score: 1 Randomisation: not stated Not blinded No dropouts reported Funding: not stated
Michetti (Italy, 1975)[59]	Unclear Mean age: 52.4 yrs 66% female	*Softener+stimulant vs softener+stimulant vs placebo* I: Droctil (50mg DSS softener + 25mg danthron). 100mg x 2 caps/day C1: DSS (.075g)+Cascara (.05g) + herbal ingredients C2: Placebo (N=35)	*Frequency* (BM/day): I=1.05, C1=1.26, C2=0.83 (Both treatments significantly different from placebo at p<0.05) *Use of laxatives (mean number of days)*: I=1.76, C1=1.73, C2=1.68 (ns) *Mean number of days with liquid stools*: Highest with C1 (DSS+cascara): 0.29 vs 1.88 vs 0.59 (p<0.05) *Pain*: Mean number of days with abdominal pain highest with C1(DSS+cascara): 0.59 vs 1.88 vs 0.77 (p<0.05) *Meteorism*: Most common with I (Droctil): 1.94 vs 3.06 vs 2.39 (p<0.05)	Quality score: 2 Randomisation: stated Not blinded No dropouts reported Funding: not stated

Key: I=Intervention, C=Comparator. BM=Bowel movements. DSS=dioctyl sodium sulfosuccinate. ITT=intention to treat. ns=not significant.

other laxatives.[43] Stimulant laxatives have previously been reported to cause abdominal cramping and diarrhoea with excessive use.[40] Adverse effects previously noted with the use of lactulose include cramping and nausea.[60,61]

E. Cost-effectiveness of laxatives

Two UK RCTs have examined the cost-effectiveness of laxative treatment. One calculated the cost per stool associated with treatment with a senna-fibre combination or with lactulose, giving a cost of 39.7p for lactulose and 10.3p per stool for a senna-fibre combination.[62,63] The senna-fibre combination was concluded to be significantly more effective in older people than lactulose, at a lower cost. Another RCT compared two osmotic agents, lactulose and sorbitol, and found them to be equally effective and similar in terms of adverse effects in the treatment of older patients.[64] The authors concluded that sorbitol is a cost-effective alternative to lactulose. A review of cost-containment strategies has noted that cost-containment primarily rests on reduction in the use of unnecessary laxatives by promoting increased fibre intake in older people.[34] However there is no formal assessment of the cost-effectiveness of this recommendation. A comparison of cost per dose for laxatives listed in the BNF is given in Table 4.[50]

F. Prevention

Three RCTs of the prevention of constipation in older people were also reviewed.[3] Two of the trials evaluated the effectiveness of bran in preventing constipation and the third evaluated the bulking agent

Table 4: Cost of laxatives[50]

* usually taken as single treatments

Classification	Preparation		Recommended dose range/day	Cost range/day
Bulk-forming laxatives	Bran	Trifyba®	7-10.5g	£0.12-£0.18
	Ispaghula Husk	Fybogel®	7g	£0.07
		Konsyl®	3.4-10.2g	£0.07-£0.21
		Isogel®	4-8g	£0.05-£0.10
		Regulan®	5.85-17.6g	£0.05-£0.15
	Methylcellulose	Celevac®	3-6g	£0.14-£0.28
	Sterculia	Normacol®	7-28g	£0.07-£0.31
		Normacol Plus®	7-28g	£0.08-£0.32
Stimulant laxatives	Bisacodyl	Bisacodyl - tablet - suppository	5-10mg 10mg*	£0.04-£0.08 £0.06*
	Dantron (danthron)	Co-danthramer	1-2 capsules	£0.21-£0.42
		Co-danthrusate	1-3 capsules	£0.21-£0.63
	Docusate Sodium	Dioctyl®	100-500mg	£0.05-£0.25
		Docusol®	100-500mg	£0.08-£0.41
		Fletchers' Enemette®	5mL*	£0.31*
		Norgalax Micro-enema®	10g*	£0.64*
	Glycerol	Glycerol Suppositories, BP	1 suppository*	£0.06*
	Senna	Senna	15-30mg	£0.03-£0.06
		Manevac®	4-8g*	£0.07-£0.14*
	Sodium Picosulfate (Sodium Picosulphate)	Sodium Picosulfate Dulco-lax®	5-10mL 5-10mg	£0.09-£0.18 £0.11-£0.22
Faecal softeners	Arachis Oil	Fletchers' Arachis Oil Retention Enema®	130mL*	£1.02*
	Liquid Paraffin	Liquid Paraffin Oral Emulsion, BP	10-30mL	£0.05-£0.15
Osmotic laxatives	Lactitol	Lactitol	20g	£0.20
	Lactulose	Lactulose	30mL	£0.15
	Macrogols	Movicol®	2-3 sachets	£0.74-£1.11
	Magnesium Salts	Magnesium Hydroxide Mixture, BP	25-50mL	£0.11-£0.22
		Liquid Paraffin and Magnesium Hydroxide Oral Emulsion, BP	5-20mL	£0.02-£0.08
		Magnesium Sulphate	5-10g	£0.01-£0.02
	Phosphates (Rectal)	Carbalax®	1 suppository*	£0.18*
		Fleet® Ready-to-use Enema	118mL*	£0.46*
		Fletchers' Phosphate Enema®	128mL*	£0.44*
	Sodium Citrate (Rectal)	Micolette Micro-enema®	5-10mL*	£0.32-£0.64*
		Micralax Micro-enema®	5mL*	£0.33*
		Relaxit Micro-enema®	5mL*	£0.32*

sterculia. None of the three RCTs found any significant benefit for the prevention of constipation. No new trials of prevention were found for this bulletin.

G. Implications

- Bulk (fibre-based) laxatives and osmotic laxatives (including lactulose and (PEG '3350') are associated with increases in frequency and improvements in stool consistency and symptoms of constipation.
- Little evidence is available at present as to the comparative effectiveness of bulk and non-bulk laxatives.
- There is no good evidence that laxatives prevent constipation in older patients.
- A stepped approach to laxative treatment would seem justified, involving initial intervention with cheaper laxatives, before proceeding to the more expensive alternatives.
- There is a pressing need for large comparative trials of different strategies for the management of constipation in adults. This should include comparisons of the effectiveness of different classes of laxatives.
- Research is also required into the effectiveness of overall dietary change (including increased fluid intake) in the treatment of constipation.

Appendix – review methods

This bulletin is based on an updated systematic review originally commissioned by the NHS HTA programme,[3] and on a review of the effectiveness of laxatives in adults.[43] The original searches were updated and extended (up to May 2001). The following databases were searched: MEDLINE, EMBASE, PsycINFO, Cochrane Library, CINAHL, International Pharmaceutical Abstracts and AMED, and the NHS Economic Evaluation Database. Other studies were obtained through contacts with laxative manufacturers and relevant experts. Individual search strategies are available on request from NHS CRD. Additional trials (originally excluded because they were in a foreign language) were also included. Two reviewers independently screened each study for inclusion. Data extraction and validity assessment were carried out by one reviewer and checked by a second. Quality assessment was based on the Jadad scale.[65] RCTs with quality scores less than 2 are tabulated but not discussed further in the text. In crossover trials, interim data were extracted where available and are reported as for a parallel RCT.

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