ClinicalEvidence

Constipation in adults

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ABSTRACT

INTRODUCTION: Although there are defined criteria for the diagnosis of constipation, in practice, diagnostic criteria are less rigid and depend in part on the perception of normal bowel habit. Constipation is highly prevalent, with approximately 12 million general practitioner prescriptions for laxatives in England in 2001. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of medications in people with idiopathic chronic constipation? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2014 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). RESULTS: At this update, searching of electronic databases retrieved 356 studies published in this time period. After deduplication, 95 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 62 studies and the further review of 33 full publications. Of the 33 full articles evaluated, three systematic reviews and one RCT were added to the overview at this update. We performed a GRADE evaluation for four PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for three interventions, based on information relating to the effectiveness and safety of linaclotide, lubiprostone, and prucalopride.

Key points

- People with idiopathic chronic constipation can be divided into two main categories: those with difficulty defecating (but with normal bowel motion frequency) and those with a transit abnormality (which can present as infrequent defecation).

  Although there are defined criteria for the diagnosis of constipation, in practice diagnostic criteria are less rigid and depend in part on the perception of normal bowel habit.

  Constipation is highly prevalent, with approximately 12 million general practitioner prescriptions for laxatives being written in England in 2001.

  Patients are often dissatisfied with laxatives, mainly due to concerns regarding their safety and efficacy.

  Emerging therapies have been tested, and meta-analyses pooling data from the relevant RCTs are reviewed in this overview.

- Lubiprostone, linaclotide, and prucalopride seem to be more effective than placebo at improving frequency of bowel movements and spontaneous complete bowel movements in people with chronic constipation.
- In terms of adverse events, lubiprostone is particularly associated with an increase in rates of nausea.
- The studies we found were conducted in secondary and tertiary care, and the patients were predominantly women; therefore, the results may not be truly applicable to all people, particularly men and patients being treated in primary care.

Clinical context

GENERAL BACKGROUND

Idiopathic chronic constipation is common, affecting up to 20% of the general population. [1]

FOCUS OF THE REVIEW

Patients are often dissatisfied with laxatives, mainly due to concerns regarding their safety and efficacy. [2] In recent years, new therapies have been developed and tested and are now available in many countries. This updated overview examines the efficacy of these new therapies.

COMMENTS ON EVIDENCE

We identified three separate meta-analyses pooling data from three RCTs of lubiprostone, three RCTs of linaclotide, and 12 RCTs of prucalopride. These RCTs were conducted in secondary and tertiary care, and the patients were

predominantly women; therefore, the results may not be truly applicable to all patients, particularly men and patients being treated in primary care. One RCT of lubiprostone, three RCTs of linaclotide, and six RCTs of prucalopride were judged as being at low risk of bias. It is important to point out that there have been no head-to-head trials of the individual drugs to summarise data from, and that individual trials used different endpoints to judge response to therapy, meaning that it is difficult to draw meaningful conclusions about the comparative efficacy of lubiprostone, linaclotide, or prucalopride.

SEARCH AND APPRAISAL SUMMARY

The updated literature search from the previous version of this overview (October 2009) was carried out to search for studies up to July 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 356 studies published in this time period. After deduplication, 95 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 62 studies and the further review of 33 full publications. Of the 33 full articles evaluated, three systematic reviews and one RCT were added at this update.

ADDITIONAL INFORMATION

All three treatments were more effective than placebo for the treatment of idiopathic chronic constipation, in terms of increasing spontaneous bowel movements to three times or more per week, and prucalopride was also more effective than placebo at increasing the proportion of stools of normal consistency. In the UK, lubiprostone and prucalopride are recommended by the National Institute for Health and Care Excellence (NICE) for patients with idiopathic chronic constipation who fail to respond to two different types of laxatives at the highest possible recommended dose, for at least 6 months, and when invasive treatment options are being considered. Linaclotide is licensed for the treatment of idiopathic chronic constipation in the US, but not in the UK.

DEFINITION

Bowel habits and perception of bowel habits vary widely within and among populations, making constipation difficult to define. People with constipation can be divided into two main categories: those with difficulty defecating (but normal bowel motion frequency) and those with a transit abnormality (which can present as infrequent defecation). The Rome III criteria is a standardised tool that diagnoses chronic constipation on the basis of two or more of the following symptoms for at least 12 weeks in the preceding 6 months: straining at defecation on at least one quarter of occasions, stools that are lumpy/hard on at least one quarter of occasions, sensation of incomplete evacuation, sensation of anorectal obstruction, or manual manoeuvres to facilitate defecation on at least one quarter of occasions, and three or less bowel movements per week. [3] In practice, however, diagnostic criteria are less rigid and are in part dependent on perception of normal bowel habit. Typically, constipation is diagnosed when a person has bowel actions twice a week or less for two consecutive weeks, especially in the presence of features such as straining at stool, abdominal discomfort, and sensation of incomplete evacuation. **Population** For the purposes of this overview, we included all RCTs stating that all participants had chronic constipation, whether or not this diagnosis was made according to strict Rome III criteria. Where the definitions of constipation in the RCTs differ markedly from those presented here, we have made this difference explicit. In this overview, we deal with chronic constipation not caused by a specific underlying disease (sometimes known as idiopathic constipation) in adults aged over 18 years, although we have included adults with pelvic floor dyssynergia. We excluded studies in pregnant women and in people with constipation associated with underlying specific organic diseases such as dehydration, autonomic neuropathy, spinal cord injury, bowel obstruction, irritable bowel syndrome, or paralytic ileus. We excluded people with Parkinson's disease and dementia, people who were postoperative, or people who were terminally ill. Opioid-induced constipation was also excluded (see overview on Constipation in people prescribed opioids). **Diagnosis** The diagnosis of constipation is initially based on history (see above). Specific tests available for further investigation include thyroid function tests, calcium concentration, colonoscopy, defecation proctogram, anorectal manometry, and colon transit time studies.

INCIDENCE/ PREVALENCE

Twelve million general practitioner prescriptions were written for laxatives in England in 2001. [4] Prevalence data are limited by small samples and problems with definition. One UK survey of 731 women found that 8.2% had constipation meeting Rome II criteria, and 8.5% defined themselves as being constipated. [5] A larger survey (1892 adults) found that 39% of men and 52% of women reported straining at stool on more than one quarter of occasions. [6] Prevalence rises in older people. Several surveys from around the world suggest that, in a community setting, prevalence among older people is about 20%. [6] [7] [8] [9] Levels of dissatisfaction with laxatives among patients with idiopathic chronic constipation are high. [2]

AETIOLOGY/ RISK FACTORS One systematic review suggested that factors associated with an increased risk of constipation included low-fibre diet and low fluid intake. One meta-analysis showed that the prevalence of constipation was higher in women (OR: 2.22; 95% CI 1.87 to 2.62) and increased with age. [1]

PROGNOSIS Untreated constipation can lead to faecal impaction (with resulting faecal incontinence), particularly in older and confused people. [10] Constipation has been suggested as a risk factor for haemorrhoids and diverticular disease; however, evidence of causality is lacking. [10]

AIMS OF INTERVENTION To relieve symptoms of constipation, to restore normal bowel habit, and to improve quality of life, with minimal adverse effects.

OUTCOMES **Frequency of bowel movements**; **stool consistency (hard/lumpy stools)**; **use of laxatives**; **adverse effects**. We have commented on additional outcomes, such as quality of life, in the Comment sections for specific interventions.

METHODS **Search strategy** *BMJ Clinical Evidence* search and appraisal July 2014. Databases used to identify studies for this overview include: Medline 1966 to July 2014, Embase 1980 to July 2014, The Cochrane Database of Systematic Reviews 2014, issue 7, the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this review were systematic reviews and RCTs published in English, at least single-blinded, and containing 20 or more individuals (10 in each arm), of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed a priori with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section, may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported questions: What are the effects of non-drug interventions in adults with idiopathic chronic constipation? What are the effects of fibre supplements in adults with idiopathic chronic constipation? What are the effects of paraffin (or similar compounds) in adults with idiopathic chronic constipation? What are the effects of osmotic laxatives in adults with idiopathic chronic constipation? What are the effects of stimulant laxatives in adults with idiopathic chronic constipation? We have added the following questions: What are the effects of medications in people with idiopathic chronic constipation? **Data and quality** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue which may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and

population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of medications in people with idiopathic chronic constipation?**

OPTION **LUBIPROSTONE**

- For GRADE evaluation of interventions for Constipation in adults, see table, p 15 .
- Lubiprostone may be more effective than placebo at decreasing treatment failure and increasing spontaneous bowel movements.
- However, absolute levels of failure to respond to treatment were still relatively high (about 45%).
- RCTs were conducted in people attending secondary and tertiary care and included mainly women, which may limit the generalisability of results to people with idiopathic chronic constipation in the general population.
- Lubiprostone may be associated with an increase in adverse effects, including nausea and diarrhoea.

Benefits and harms

Lubiprostone versus placebo:

We found one systematic review (search date 2010). [11] The review included adults (>90% of people >16 years) with idiopathic chronic constipation and a trial duration of at least 1 week. The RCTs had to report either a dichotomous evaluation of overall response, or continuous data with regard to mean number of stools per week. The review included three double-blind RCTs (129 people, 244 people, 237 people), which were all conducted in secondary and tertiary care (range from 8–20 sites), and all the trials used modified Rome II diagnostic criteria and negative investigations. The duration of treatment in the trials ranged from 3 to 4 weeks, and one RCT compared three different doses of lubiprostone versus placebo (see Further information on studies). The review reported an ITT analysis. [11] We found one subsequent double-blind RCT (170 people in Japan). [12] It included people with idiopathic chronic constipation, defined as a subpopulation of the Rome III-defined functional bowel disorders with constipation, and compared three different doses of lubiprostone versus placebo. The RCT included 42 people who also had irritable bowel syndrome (IBS), which is outside the inclusion criteria of this review. We have, therefore, only reported the subgroup analysis presented for the remaining 128 people who did not have IBS (see Further information on studies). [12]

Frequency of bowel movement

Lubiprostone compared with placebo Lubiprostone may be more effective than placebo at reducing treatment failure and increasing spontaneous bowel movements in people with idiopathic chronic constipation (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of bowel movement					
[11] Systematic review	People (>90% aged >16 years) with idiopathic chronic constipation (modified Rome II criteria and negative investigations) 3 RCTs in this analysis	**Failure to respond to therapy (response defined as increase to 3 or more spontaneous bowel movements [SBMs] per week from baseline [1 RCT]; 3 or more SBMs per week [1 RCT]; or 4 or more SBMs per week [1 RCT])** 151/335 (45%) with lubiprostone 184/275 (67%) with placebo	RR 0.67 95% CI 0.56 to 0.80 P <0.0001 NNT 4 95% CI 3 to 7 See Further information on studies	●○○	lubiprostone
[12] RCT **4-armed trial**	People, average age about 40 years, with idiopathic chronic constipation Sub-group analysis of people with constipation without IBS	**Changes in the weekly average number of SBMs from baseline , at 1 week** with highest-dose lubiprostone with placebo Absolute results reported graphically 63 people in this analysis	P <0.01 Results were also significant at 2 weeks (P <0.01) *Post hoc* analysis	○○○	lubiprostone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		3 arms included different doses of lubiprostone; the fourth arm was placebo			
[12] RCT **4-armed trial**	People, average age about 40 years, with idiopathic chronic constipation Sub-group analysis of people with constipation without IBS	**Changes in the weekly average number of SBMs from baseline, at 1 week** with middle-dose lubiprostone with placebo Absolute results reported graphically 64 people in this analysis 3 arms included different doses of lubiprostone; the fourth arm was placebo	P <0.01 Results were also significant at 2 weeks (P <0.05) *Post hoc* analysis	○○○	lubiprostone
[12] RCT **4-armed trial**	People, average age about 40 years, with idiopathic chronic constipation Sub-group analysis of people with constipation without IBS	**Changes in the weekly average number of SBMs from baseline, at 1 week** with lowest-dose lubiprostone with placebo Absolute results reported graphically 63 people in this analysis 3 arms included different doses of lubiprostone, the fourth arm was placebo	Reported as P <0.1 Results were not significant at 2 weeks (P value not reported) *Post hoc* analysis	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	People (>90% aged >16 years) with idiopathic chronic constipation (modified Rome II criteria and negative investigations) 3 RCTs in this analysis	**Total number of adverse events** with lubiprostone with placebo Absolute results not reported	RR 1.79 95% CI 1.21 to 2.65 NNH = 4 95% CI 3 to 6	●○○	placebo
[11] Systematic review	People (>90% aged >16 years) with idiopathic chronic constipation (modified Rome II criteria and negative investigations) 3 RCTs in this analysis	**Diarrhoea** with lubiprostone with placebo Absolute results not reported	RR 4.46 95% CI 1.28 to 15.48	●●○	placebo
[11] Systematic review	People (>90% aged >16 years) with idiopathic chronic constipation (modified Rome II criteria	**Nausea** with lubiprostone with placebo Absolute results not reported	RR 7.27 95% CI 3.76 to 14.06	●●●	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	and negative investigations) 3 RCTs in this analysis				
[12] RCT **4-armed trial**	People, average age about 40 years, with idiopathic chronic constipation	**At least 1 adverse event** 17/44 (39%) with highest-dose lubiprostone 13/43 (30%) with middle-dose lubiprostone 1/41 (2%) with lowest-dose lubiprostone 2/42 (5%) with placebo Includes people with constipation with and without IBS	P value among groups not reported		
[12] RCT **4-armed trial**	People, average age about 40 years, with idiopathic chronic constipation	**Diarrhoea** 8/44 (18%) with highest-dose lubiprostone 4/43 (9%) with middle-dose lubiprostone 0/41 (0%) with lowest-dose lubiprostone 0/42 (0%) with placebo Includes people with constipation with and without IBS	P value among groups not reported Incidence of diarrhoea significantly higher in highest-dose arm *v* placebo (P = 0.0037) and middle dose arm *v* placebo (P = 0.0429) No other pairwise analysis reported	○○○	placebo compared with highest-dose and middle-dose lubiprostone
[12] RCT **4-armed trial**	People, average age about 40 years, with idiopathic chronic constipation	**Nausea** 7/44 (16%) with highest-dose lubiprostone 3/43 (7%) with middle-dose lubiprostone 0/41 (0%) with lowest-dose lubiprostone 0/42 (0%) with placebo	P value among groups not reported Incidence of nausea significantly higher in highest-dose arm *v* placebo (P = 0.007) No other pairwise analysis reported	○○○	placebo compared with highest-dose lubiprostone

Lubiprostone versus linaclotide:

We found no RCTs.

Lubiprostone versus prucalopride:

We found no RCTs.

Further information on studies

[11] The review noted that two of the three included RCTs had unclear randomisation and allocation concealment, although one trial (244 people) was at low risk of bias. [11] It reported that none of the RCTs reported extractable data on mean stools per week or on individual symptoms, and it was unable to perform a pre-specified sensitivity analysis. [11] The review noted that overall, none of the trials included participants in primary care (all the 3 RCTs comparing lubiprostone with placebo were in secondary and tertiary care), so results may not be truly generalisable to people with constipation consulting their GP. The three RCTs included predominantly female participants (88%; 90%; 91%), which may also affect the generalisability of the results.

[12] The RCT included people with less than three defecations per week and at least one of three other criteria of functional constipation (lumpy or hard stools in at least 25% of defecations; sensation of incomplete evacuation for at least 25% of defecations; straining during at least 25% of defecations), which lasted for more than 6 months. [12] The majority of participants were female (91%). The method of randomisation and allocation concealment was not described, the RCT was described as double-blinded, and one author was an employee of the pharmaceutical company that sponsored the trial.

Comment: All three RCTs included from the systematic review [11] showed that lubiprostone may be effective at increasing spontaneous bowel movements to three or more times per week in people with idiopathic chronic constipation. One trial was at low risk of bias. Generalisability of these trials may be limited, as the participants were recruited from secondary and tertiary care, and were predominantly women (88%–91%).

Clinical guide

Lubiprostone is available in the US and the EU. According to the National Institute for Heath and Care Excellence (July 2014), lubiprostone is recommended for people with idiopathic chronic constipation who fail to respond to two different types of laxatives at the highest possible recommended dose, for at least 6 months, and when invasive treatment would otherwise be the only option. [13]

OPTION LINACLOTIDE New

- For GRADE evaluation of interventions for Constipation in adults, see table, p 15 .
- Linaclotide may be more effective than placebo at decreasing treatment failure and increasing complete spontaneous bowel movements.
- However, absolute levels of failure to respond to therapy were quite high (about 80%).
- RCTs were conducted in people attending secondary and tertiary care and included mainly women, which may limit the generalisability of results to people with idiopathic chronic constipation in the general population.
- Linaclotide may be associated with an increase in adverse effects including diarrhoea.

Benefits and harms

Linaclotide versus placebo:

We found two systematic reviews, which included slightly different trial reports of the same RCTs and reported slightly different analyses, so we have presented results from both. [11] [14] The first systematic review (search date 2010) [11] included trials that reported either a dichotomous outcome assessment of overall response to treatment or mean number of stools per week during therapy (see option on Lubiprostone, p 4). It included 1582 people in the analysis from three RCTs that had used modified Rome II criteria, one of which had also used negative colonoscopy within the last 10 years. The RCTs were undertaken in secondary and tertiary care. It reported on overall response to treatment, and treatment duration ranged from 4 to 12 weeks. The second review (search date 2012) [14] included 1663 people in the analysis from three RCTs; they reported on the improvement from baseline in complete spontaneous bowel movements per week, and reported results separately for two doses of linaclotide that had been approved for use by the FDA.

Frequency of bowel movement

Linaclotide compared with placebo Linaclotide seems to be more effective than placebo at reducing treatment failure and increasing complete spontaneous bowel movements in people with idiopathic chronic constipation (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of bowel movement					
[11] Systematic review	People (>90% aged >16 years) with idiopathic chronic constipation (modified Rome II criteria)	**Failure to respond to therapy (response defined as 3 or more complete spontaneous bowel movements [CSBMs] and an increase of 1 or more relative to baseline for 75% of treatment weeks)**	RR = 0.84 95% CI 0.80 to 0.87 P <0.00001 NNT = 6 95% CI 5 to 8	●○○	linaclotide

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	3 RCTs in this analysis	860/1089 (79%) with linaclotide 468/493 (95%) with placebo			
[14] Systematic review	People, mean age 46.9 years, with idiopathic chronic constipation (modified Rome II criteria) 3 RCTs in this analysis	**Improvement in bowel symptoms (3 or more CSBMs weekly and increase of 1 or more CSBM/week from baseline for 75% or more weeks)** 95/486 (20%) with lower-dose linaclotide 25/492 (5%) with placebo	RR 3.80 95% CI 2.20 to 6.55 P <0.00001 NNT = 7 95% CI 5 to 12	●●○	linaclotide
[14] Systematic review	People, mean age 46.9 years, with idiopathic chronic constipation (modified Rome II criteria) 3 RCTs in this analysis	**Improvement in bowel symptoms (3 or more CSBMs weekly and increase of 1 or more CSBM/week from baseline for 75% or more weeks)** 105/480 (22%) with higher-dose linaclotide 25/492 (5%) with placebo	RR 4.26 95% CI 2.80 to 6.47 P <0.00001 NNT = 7 95% CI 5 to 8	●●○	linaclotide

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	People (>90% aged >16 years) with idiopathic chronic constipation (modified Rome II criteria) Data from 1 RCT	**Total adverse event rates** 34% with linaclotide 32% with placebo Absolute numbers not reported	Significance not reported		
[11] Systematic review	People (>90% aged >16 years) with idiopathic chronic constipation (modified Rome II criteria) 3 RCTs in this analysis	**Diarrhoea** with linaclotide with placebo Absolute results not reported	RR 3.08 95% CI 1.27 to 7.48	●●○	placebo
[14] Systematic review	People, mean age 46.9 years, with idiopathic chronic constipation (modified Rome II criteria) 3 RCTs in this analysis	**Diarrhoea** with lower-dose linaclotide with placebo Absolute results not reported	RR 2.19 95% CI 0.5 to 9.48	⟷	Not significant
[14] Systematic review	People, mean age 46.9 years, with idiopathic chronic constipation (modified Rome II criteria) 3 RCTs in this analysis	**Diarrhoea** 63/494 (13%) with higher-dose linaclotide 22/503 (4%) with placebo	RR 2.84 95% CI 1.78 to 4.54	●●○	placebo

Linaclotide versus lubiprostone:

We found no RCTs.

Linaclotide versus prucalopride:

We found no RCTs.

Further information on studies

[11] The review reported that all three RCTs were at low risk of bias and none reported extractable data on the mean number of stools per week. The review noted that the three RCTs included participants from secondary and tertiary care, and included mainly women (89%; 89%; 92%), which may affect the generalisability of results (see option on Lubiprostone, p 4). The review reported that one RCT (310 people) found that linaclotide also led to a significantly higher proportion of people with decreased severity of abdominal discomfort and bloating (further details not reported).

[14] The review also reported improvement in abdominal discomfort and bloating (measured by improvement of 0.5 or more from baseline on 1–5 scale for 75% or more weeks). The review found that both doses of linaclotide significantly improved abdominal discomfort and bloating compared with placebo (abdominal discomfort responder: lower dose, 3 RCTs, 978 people, RR 1.57, 95% CI 1.26 to 1.97; higher dose, 3 RCTs, 972 people, RR1.66, 95% CI 1.34 to 2.08; bloating responder: lower dose, 3 RCTs, 978 people, RR 1.97, 95% CI 1.44 to 2.69; higher dose, 3 RCTs, 972 people, RR 1.91, 95% CI 1.50 to 2.44). The review reported that all authors of all studies included in the meta-analysis were employees or paid consultants for the developer and manufacturer of linaclotide, although the results were confirmed by a third party statistician. [14]

Comment: All three RCTs demonstrated that linaclotide may be effective at increasing spontaneous bowel movements to three times a week or more in people with idiopathic chronic constipation. All three trials were at low risk of bias. Generalisability of these trials may be limited as the participants were recruited from secondary and tertiary care, and were predominantly females (89%–92%).

Clinical guide

Linaclotide is licensed in the US for both idiopathic chronic constipation and irritable bowel syndrome with constipation (IBS). However, in the UK linaclotide is currently only licensed for IBS with constipation, and not for idiopathic chronic constipation.

OPTION PRUCALOPRIDE

- For GRADE evaluation of interventions for Constipation in adults, see table, p 15 .
- Prucalopride may be more effective than placebo at decreasing treatment failure and increasing spontaneous bowel movements.
- However, absolute levels of failure to respond to therapy were quite high (about 70%).
- Trials were conducted in people attending secondary and tertiary care and included predominantly women, which may limit the generalisability of results to people with idiopathic chronic constipation in the general population.
- Prucalopride may be associated with an increase in adverse effects including diarrhoea, nausea, and headache.

Benefits and harms

Prucalopride versus placebo:

We found two systematic reviews, which reported different analyses, so both are presented below. [11] [15] The first systematic review (search date 2010) [11] included trials that reported either a dichotomous outcome assessment of overall response to treatment or mean number of stools per week during therapy (see option on Lubiprostone, p 4). It included 2639 people in the analysis from seven RCTs, six of which had used modified Rome II criteria, one with negative investigations. Six RCTs were undertaken in secondary and tertiary care, while one RCT did not report its setting. Treatment duration ranged from 4 to 12 weeks. Two RCTs recruited people either resistant to or dissatisfied

with laxatives, and only one trial recruited people aged over 65 years. The second systematic review (search date 2013) included 11 RCTs with a treatment duration of 1 to 12 weeks. [15] Six RCTs were included in the first review, two RCTs were subsequent to the first review, and it included three RCTs not included in the first review. In one RCT published subsequent to the first review (240 women), the control group was PEG3350 rather than placebo. The review contacted authors of the RCTs to obtain additional information on study outcomes.

Frequency of bowel movement

Prucalopride compared with placebo Prucalopride may be more effective than placebo at reducing treatment failure and increasing spontaneous bowel movements in people with idiopathic chronic constipation (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of bowel movement					
[11] Systematic review	Adults (at least 90% over the age of 16 years) diagnosed with idiopathic chronic constipation (mostly with modified Rome II criteria) 7 RCTs in this analysis	**Failure to respond to therapy (response defined as 3 or more complete spontaneous bowel movements [CSBMs] per week [5 RCTs], 3 or more stools per week [1 RCT], or effect moderate or above as rated by investigator [1 RCT])** 1288/1796 (72%) with prucalopride 731/843 (87%) with placebo	RR 0.82 95% CI 0.76 to 0.88 P <0.00001 NNT = 6 95% CI 5 to 9 Significant heterogeneity between studies (I^2 = 60%, P for heterogeneity 0.02; this was examined by sensitivity analysis — see Further information on studies)	●○○	prucalopride
[15] Systematic review	Adults (18 years of age or older) with chronic constipation 9 RCTs in this analysis	**Mean of 3 or more spontaneous bowel movements (SBMs) per week** 610/2111 (29%) with prucalopride 227/1214 (19%) with control	RR 1.63 95% CI 1.07 to 2.49 P = 0.02 Significant heterogeneity between studies (I^2 = 89%, P for heterogeneity <0.00001; see Further information on studies) The analysis included 8 placebo-controlled RCTs and 1 RCT (240 people) that used PEG3350 as a control Visual inspection of the forest plot suggests that this RCT had a different direction of effect than the placebo-controlled trials	●○○	prucalopride
[15] Systematic review	Adults (aged 18 years or older) with chronic constipation 9 RCTs in this analysis	**Mean of 1 or more SBM per week improvement** 996/2111 (47%) with prucalopride 379/1214 (31%) with control	RR 1.58 95% CI 1.18 to 2.12 P = 0.002 Significant heterogeneity between studies (I^2 = 89%, P for heterogeneity <0.00001; see Further information on studies) The analysis included 8 placebo-controlled RCTs and 1 RCT (240 people) that used PEG3350 as a control Visual inspection of the forest plot suggests that this RCT had a different direction of effect than the placebo-controlled trials	●○○	prucalopride

Stool consistency (hard/lumpy stools)

Prucalopride versus placebo Prucalopride may be more effective than placebo at increasing the proportion of bowel movements with normal consistency in people with idiopathic chronic constipation (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Stool consistency					
[15] Systematic review	Adults (aged 18 years or older) with chronic constipation 6 RCTs in this analysis	**Mean difference for proportion of bowel movements of normal consistency (normal consistency not further defined)** with prucalopride with control Absolute results not reported 2661 people in this analysis	Mean difference 9.16% 95% CI 7.28% to 11.03% Significant heterogeneity between studies (I^2 = 88%, P for heterogeneity <0.00001; see Further information on studies) The analysis included 5 placebo-controlled RCTs and 1 RCT (240 people) that used PEG3350 as a control	○○○	prucalopride

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	Adults (at least 90% over the age of 16 years) diagnosed with idiopathic chronic constipation (mostly with modified Rome II criteria) 6 RCTs in this analysis	**Total number of adverse events** with prucalopride with placebo Absolute results not reported	RR 1.14 95% CI 1.05 to 1.24	●○○	placebo
[11] Systematic review	Adults (at least 90% over the age of 16 years) diagnosed with idiopathic chronic constipation (mostly with modified Rome II criteria) 6 RCTs in this analysis	**Serious adverse events** with prucalopride with placebo Absolute results not reported	RR 0.88 95% CI 0.58 to 1.34 There was 1 episode of supraventricular tachycardia in the prucalopride group; no other cardiovascular events were reported	⟷	Not significant
[11] Systematic review	Adults (>90% aged >16 years) diagnosed with idiopathic chronic constipation (mostly with modified Rome II criteria) 6 RCTs in this analysis	**Diarrhoea** with prucalopride with placebo Absolute results not reported	RR 2.72 95% CI 1.80 to 4.13	●●○	placebo
[11] Systematic review	Adults (>90% aged >16 years) diagnosed with idiopathic chronic constipation (mostly with modified Rome II criteria) 6 RCTs in this analysis	**Nausea** with prucalopride with placebo Absolute results not reported	RR 1.98 95% CI 1.39 to 2.82	●○○	placebo
[11] Systematic review	Adults (>90% aged >16 years) diagnosed with idiopathic chronic constipa-	**Headache** with prucalopride with placebo	RR 1.70 95% CI 1.25 to 2.31	●○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	tion (mostly with modified Rome II criteria) 6 RCTs in this analysis	Absolute results not reported			

Prucalopride versus lubiprostone:

We found no RCTs.

Prucalopride versus linaclotide:

We found no RCTs.

Further information on studies

[11] The systematic review found significant heterogeneity between studies and conducted a pre-specified sensitivity analysis. The results were no longer heterogeneous when only RCTs that used three or more complete spontaneous bowel movements (CSBMs) per week as an outcome were included (5 RCTs, 2509 people, RR of failure to respond to therapy 0.84, 95% CI 0.80 to 0.88), when trials with only a low risk of bias were included (3 RCTs, 1564 people, RR of failure to respond to therapy 0.84, 95% CI 0.79 to 0.89), or when trials using modified Rome II criteria only were included (6 RCTs, 2562 people, RR of failure to respond to therapy 0.84, 95% CI 0.81 to 0.88).

[11] The review reported that three trials were at low risk of bias, and in four RCTs randomisation and concealment of allocation was unclear. It reported that the effect on individual symptoms was not reported in any of the included RCTs.

[15] The review reported that there was substantial heterogeneity observed in all analyses, which was attributable, in part, to the inclusion of an RCT that used PEG3350 as control.

[15] The review also reported on Patient Assessment of Constipation quality of life scores (PAC-QOL) and patient symptoms (PAC-SYM). It found that prucalopride significantly improved both PAC-QOL and PAC-SYM scores (by 1 or more) compared with control (PAC-QOL: 6 RCTs, 3021 people, RR 1.51, 95% CI 1.07 to 2.11; significant heterogeneity in analysis, I^2 91%; PAC-SYM: 6 RCTs, 3021 people, RR 1.47, 95% CI 1.10 to 1.98; significant heterogeneity in analysis, I^2 83%; one RCT [240 people] included PEG3350 as control rather than placebo in both analyses).

[15] The review reported that limitations included inconsistencies in the reporting of outcomes across studies, only one RCT was in older people, and most trials included mainly women.

Comment:

Particular attention has been paid to potential prolongation of the QTc interval since this was an issue with the 'precursor' drug, cisapride. No concerns have emerged, so far, regarding cardiac safety. The standard dose of 2 mg once daily may be too high for some patients, particularly in the higher age group and, therefore, a 1 mg starting dose is advised in older people. However, some patients may need 4 mg in order to obtain an optimal effect.

Twelve RCTs in total showed that prucalopride may be effective at increasing spontaneous bowel movements to three times or more per week, and increasing the proportion of stools of normal consistency in people with idiopathic chronic constipation. Six trials were at low risk of bias. Generalisability of these trials may be limited as the participants were recruited from secondary and tertiary care, and were predominantly females (70%–100%).

Clinical guide
According to the National Institute for Health and Care Excellence (2010), prucalopride is recommended for women with idiopathic chronic constipation who have failed to respond to at least two different types of laxatives at the highest tolerated doses, for at least 6 months, and where invasive treatment is being considered. [16]

Prucalopride is a 5-HT4 receptor agonist. Its receptor specificity seems much higher than that of the previously developed compounds of this class. [17] As prucalopride seems to stimulate propulsive motility in the entire GI tract, efficacy in conditions other than constipation is to be expected. Currently, prucalopride is approved by the European Medicines Agency (EMA) for women only, as the small numbers of men included in the trials lead to borderline statistical significance in the male subgroups. However, the numerical data are nearly identical for the sexes. A trial studying the effects of prucalopride in males has been conducted, and reported in abstract form, and the fully published results are expected soon.

GLOSSARY

Rome II criteria (updated 1999) Rome criteria for constipation require two or more of the following symptoms to be present for at least 12 weeks out of the preceding 12 months: straining at defecation on at least a quarter of occasions; stools are lumpy/hard on at least a quarter of occasions; sensation of incomplete evacuation on at least a quarter of occasions; and three or fewer bowel movements a week. [18]

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Rome III criteria Rome III criteria for constipation require two or more of the following symptoms for at least 12 weeks in the preceding 6 months: straining at defecation on at least one quarter of occasions, stools that are lumpy/hard on at least one quarter of occasions, sensation of incomplete evacuation, sensation of anorectal obstruction, or manual manoeuvres to facilitate defecation on at least one quarter of occasions, and three or less bowel movements per week. [3]

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Linaclotide New option. Two systematic reviews added. [11] [14] Categorised as 'likely to be beneficial'.

Lubiprostone One systematic review [11] and one RCT [12] added. Categorisation unchanged (likely to be beneficial).

Prucalopride Two systematic reviews added. [11] [15] Categorisation unchanged (likely to be beneficial).

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Disclaimer

GRADE **Evaluation of interventions for Constipation in adults.**

Important outcomes	Frequency of bowel movement, Stool consistency (hard/lumpy stools)								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of medications in people with idiopathic chronic constipation?									
4 (673) [11] [12]	Frequency of bowel movement	Lubiprostone versus placebo	4	–2	0	–1	0	Very low	Quality point deducted for weak methods and incomplete reporting of results; directness point deducted for unclear generalisability (mainly women, set in secondary and tertiary care)
3 (at least 1582) [11] [14]	Frequency of bowel movement	Linaclotide versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for unclear generalisability (mainly women, set in secondary and tertiary care)
7 / at least 9 (2369 / at least 3325) [11] [15]	Frequency of bowel movement	Prucalopride versus placebo	4	0	–1	–1	0	Low	Consistency point deducted for significant heterogeneity; directness point deducted for unclear generalisability (mainly women, set in secondary and tertiary care)
6 (2661) [15]	Stool consistency (hard/lumpy stools)	Prucalopride versus placebo	4	0	–1	–1	0	Low	Consistency point deducted for significant heterogeneity; directness point deducted for unclear generalisability (mainly women, set in secondary and tertiary care)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.