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SYSTEMATIC REVIEW

Cost Effectiveness of Treatments for Chronic Constipation: A Systematic Review

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Abstract

Background Chronic constipation (CC) has a significant impact on patients' quality of life and imposes an economic burden on individuals and the healthcare system. Treatment options include dietary changes, lifestyle modifications, fibre supplements, stool softeners, and laxatives.

Objective We undertook this systematic review to comprehensively evaluate the cost effectiveness of treatments for CC.

Methods We searched ten common databases to identify economic evaluations published to 13 June 2017. Abstract and full-text review were completed in duplicate. The quality of the included studies was assessed using the Consensus on Health Economic Criteria. Data extracted included costs and outcomes of treatments for CC and cost-effectiveness methods. A narrative synthesis was completed.

Results From the 4338 unique citations identified, 79 proceeded to full-text review, with 10 studies forming the final dataset. Eight different definitions of CC were used to define the study populations. Study designs used were decision-tree models (4), Markov model (1), and retrospective (1) and prospective (4) studies. Quality-adjusted life-years (QALY) were reported in five studies; other outcomes included, discontinuation of laxative treatment and frequency of bowel movements. The majority of studies stated that their results were from a payer perspective; however, some of these studies only considered treatment costs, a subset of costs included in the payer perspective. Lifestyle advice, dietary treatments and abdominal massage were each compared with current care with laxatives, while polyethylene glycol (PEG) and senna–fibre combination were each compared with lactulose. Two studies compared newer treatments in patients who had not responded to laxatives: prucalopride was compared with continuing laxatives, and linaclotide was compared with lubiprostone. All of the interventions were reported by the study authors to be cost effective, with the exception of abdominal massage.

Conclusions A consistent definition of CC is needed and the QALY should be used to capture the diverse symptoms of CC. Further analysis is needed comparing all available treatments for patients who have not responded to laxatives. Overall, results from economic evaluations appear to align with stepwise practice guidelines.

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Key Points for Decision Makers

In the economic evaluations of treatments in chronic constipation (CC) there is heterogeneity in the definition of CC and outcome measures assessed.

The review found that dietary/lifestyle modifications were cost effective or cost saving compared with laxatives alone.

There is limited cost-effectiveness evidence comparing treatments for patients who have not responded to laxatives.

The factors that had the most impact on cost effectiveness of treatment for CC were the effectiveness of treatment and probability of discontinuation or switching to another laxative.

1 Introduction

Constipation is a worldwide problem that is common across all ages and cultures and is the cause of considerable morbidity. It is often considered to be synonymous with infrequent bowel movements, usually fewer than three per week, however symptoms might also include hard stools, a feeling of incomplete evacuation, abdominal discomfort, bloating and distention [1]. With chronic constipation (CC), often referred to as idiopathic or functional, no obvious endocrinological, neurological, iatrogenic, or other causes have been identified [2]. As CC is a symptom-based disorder without a universally employed definition, its true prevalence is unknown. Reported prevalence rates have ranged from 2 to 27% in the Western world [2, 3], and it is estimated only one-third of those affected with CC ever seek medical care [2]. CC is associated with advancing age, being female, inactivity, low calorie intake, polypharmacy, low income, low education level, depression, and abuse [1, 2, 4].

CC is not a benign, easily treated condition. The disorder lowers one's quality of life while imposing an economic burden on both the individual and society [5]. Individuals may experience anxiety, depression, somatization, and sexual dysfunction, and CC has also resulted in absenteeism and loss of productivity at work and school [2]. The economic impacts of CC include costs related to diagnosis, treatment, and management, as well as CC-related comorbidities (haemorrhoids/anal fissures, and ileus/volvulus) [5, 6]. In a study based on national healthcare visit surveys, it was shown that CC results in more than 2.5 million hospital and physician visits per year in the US [6]. The estimated annual expenditure on laxatives was US$500–$800 million by doctors via prescriptions, with more than an additional $200 million in over-the-counter products [3]. For diagnosed patients, direct medical costs were estimated to be $250–$500 per patient in the US, with out-of-pocket expenses of approximately US$400 per patient per year [6].

Various treatment options for CC are available. Although effectiveness varies, these treatments include dietary changes (increasing dietary fibre), lifestyle modifications (e.g. aerobic exercise), and the use of fibre supplements (bulking agents such as bran), stool softeners, and laxatives [2, 3]. The goal of treatment for patients with CC is global relief of constipation symptoms and a return to normal bowel function [7]. Most cases of CC are managed with a symptomatic graded approach [1, 8]. The American Gastroenterological Association suggests that patients start with a gradual increase in fibre intake both from foods included in the diet and from supplements. An osmotic laxative such as polyethylene glycol (PEG) or milk of magnesia is a recommended alternative, or for use in combination with increased fibre intake. If treatment success is not achieved after use with osmotic laxatives then stimulant laxatives such as bisacodyl or glycerin suppositories are recommended [8]. A newer agent should be considered when symptoms are not responsive to laxatives, including drugs such as lubiprostone and linaclotide; another agent, prucalopride, is not available in the US but has been approved in other countries [8]. Non-pharmaceutical therapies include massage, biofeedback therapy or surgical treatment.

Providing effective and cost-effective treatment is essential for both public and private healthcare systems. To date, no study has reviewed cost-effectiveness literature in CC using a formal systematic review approach. In order to better inform decision makers and clinicians, the objective of this study was to synthesize evidence by conducting a systematic review of economic evaluations of treatments for CC and assess the quality of these studies.

2 Methods

2.1 Eligibility Criteria

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines by Moher et al. [9] were followed for the review and reporting procedures. Studies eligible for inclusion represented full economic evaluations [i.e. cost-effectiveness analyses (CEAs), cost-utility analyses (CUAs), or cost-consequences analysis (CCA)] that evaluated a treatment for CC. Studies with partial economic evaluations, or cost-minimization analyses (CMAs) or cost-of-illness studies were excluded, as

were studies that did not compare at least one active treatment for CC. Studies were required to report both costs and effectiveness outcomes. Research articles published in the English language were included, while comments, editorials, letters, news, correspondence, study protocols, case reports, case series, and narrative and systematic reviews were excluded.

2.2 Information Sources and Search

MEDLINE (to June 2017), EMBASE (to June 2017), CINAHL, Web of Science, HTA database (to fourth quarter 2016), NHS Economic Evaluation Database (to first quarter 2016), DARE (to first quarter 2016), Cochrane Database of Systematic Reviews (to June 2017), Cochrane Registry of Controlled Trials (to April 2017), and EconoLIT (to June 2017) were searched. The database searches were developed by a research librarian (DL) and run by one of our researchers (DH). Search concepts were economic evaluations and constipation. The last search was run on 13 June 2017. Manufacturers or study authors were not contacted to identify any other unpublished sources of information. Strategies for each database searched can be found in Appendix A (see electronic supplementary material).

2.3 Study Selection

Two authors (DH and ES) independently screened all titles and abstracts. The full text of the eligible articles was retrieved and reviewed independently by two authors (DH and ES) and a study was included for final review if it met all of the eligibility criteria (Fig. 1). Discrepancies were discussed by both reviewers until a consensus was reached regarding eligibility.

2.4 Data Collection Process and Data Items

Details from each of the studies were extracted into an evidence table. Extracted variables included author, country, study population, study characteristics (e.g. perspective, time horizon, discount rate, model type, and sensitivity analysis), treatment (e.g. drug, dosage), source of effectiveness data, resource use and source of cost data, funding sources, cost outcomes, effectiveness outcomes, incremental cost-effectiveness ratio (ICER), author's conclusions, and limitations. Data extraction was conducted by one author (DH) and verified by another (NI).

2.5 Quality Assessment

The 19-item, internationally accepted Consensus on Health Economic Criteria (CHEC) list, a criteria list for quality assessment of economic evaluations that can be used in systematic reviews, was used to assess the quality of the included studies [10]. This list includes yes or no questions on the methodological quality of economic evaluations, such as the appropriateness of the population, competing alternatives, perspective, and valuing of cost. Two authors (DH and NI) independently reviewed the studies and scored each question as 1 (yes) or 0 (no). Any discrepancies were discussed by both reviewers, in consultation with a third reviewer (ES). The proportion of studies meeting each item of the CHEC list was determined.

3 Results

3.1 Study Selection

A total of 6460 citations were found through the electronic database search process; approximately 33% ($n = 2122$) were duplicate citations and were removed from further review. Of the remaining 4338 citations, 98% ($n = 4259$) of the titles and abstracts were deemed ineligible during the screening process as they were not economic evaluations. Of the 79 papers that qualified for a full-text review, 2 were not available for review and 67 did not meet the study eligibility criteria. The flowchart in Fig. 1 outlines the search results, indicating exclusions at various stages of the review process. Overall, 10 publications were included in this systematic review (Tables 1 and 2) [11–20]. We have summarized the findings of these studies by type of treatment: non-pharmacological interventions (two studies) [14, 19], laxatives (six studies) [11, 13, 16–18, 20], and newer agents (two studies) [12, 15].

3.2 Study Description by Treatment Type

3.2.1 Non-Pharmacological Interventions (n = 2)

Non-pharmacological interventions assessed in economic evaluations included dietary and lifestyle advice (consultation with/without telephone reinforcement) and abdominal massage (self or professional) [14, 19]. Speed et al. [14] reported on the LIFELAX trial—diet and lifestyle versus laxatives in the management of CC in older people in the UK. Patients recruited for the LIFELAX trial were those who were prescribed laxatives three or more times in the previous 12 months or had a recorded diagnosis of functional constipation. A CCA was undertaken from a health service perspective in the UK. They reported on two constipation-specific measures, as well as discomfort-free days and EQ-5D (EuroQol five-dimensions questionnaire). No statistically significant differences in health outcomes were reported between diet and lifestyle versus laxatives. LIFELAX was reported to have lower costs than

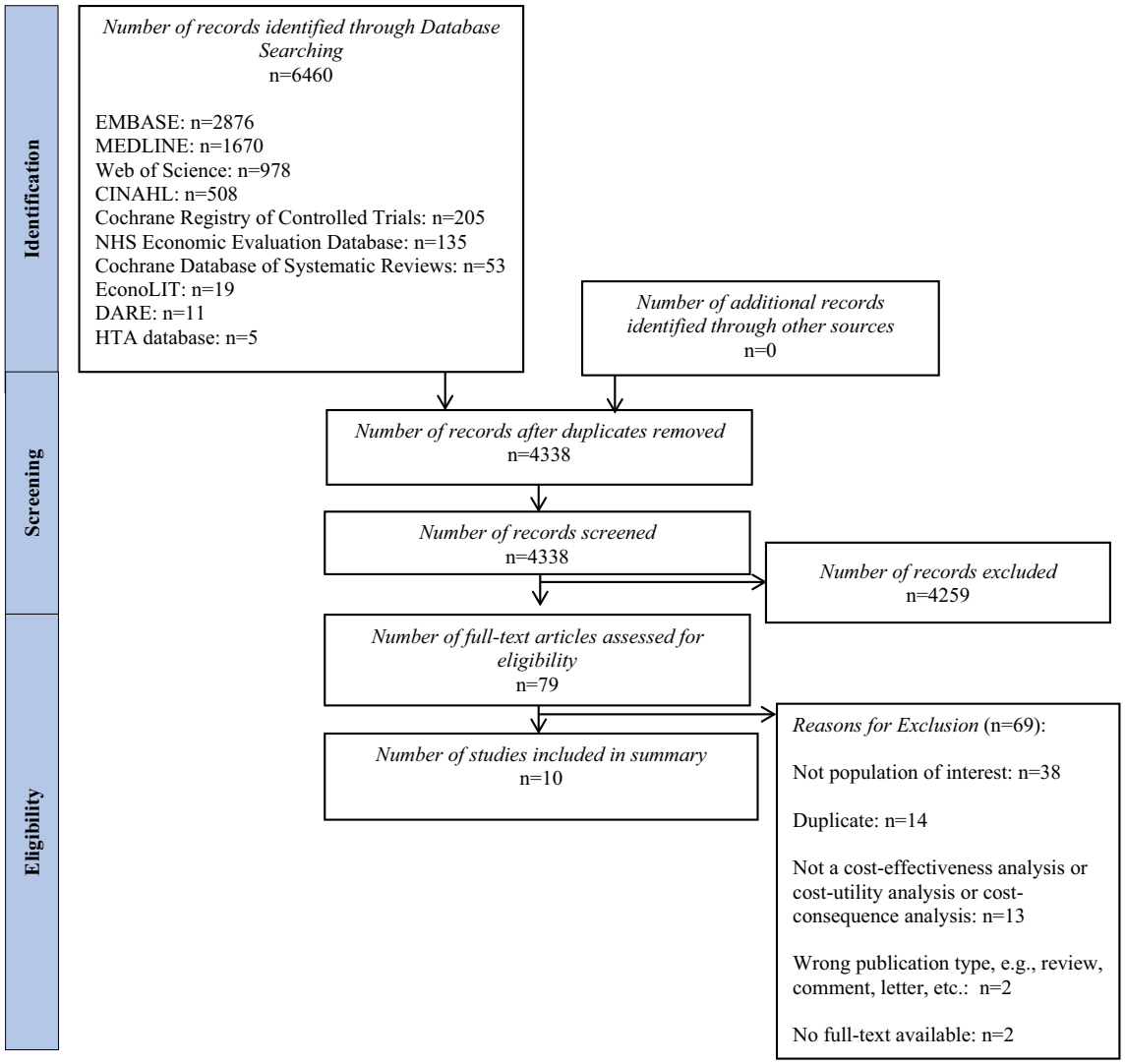

Fig. 1 PRISMA-modelled flowchart of the screening and eligibility evaluation phases

unspecified laxative use due to lower general practitioner (GP) and hospital visits, although GP telephone consultancies and practice nurse use was higher. Lämås et al. [19] conducted a non-blinded, randomized controlled trial (conducted between January 2005 and March 2007) of 60 patients with constipation as defined by the Rome II criteria [21]. Data were collected over 16 weeks. They compared continued laxative use with self or professional abdominal massage. From a societal perspective, the cost per quality-adjusted life-year (QALY) of the self-massage intervention compared with laxatives was €75,000, which included therapist travel and overhead costs, as well as patient time and travel costs. For the professional massage intervention, the cost per QALY compared with laxatives was €60,000, not including therapist travel and overhead costs.

3.2.2 Newer Agents (n = 2)

Two studies evaluated newer agents; comparisons included prucalopride versus continued laxatives, and linaclotide versus lubiprostone [12, 15]. Patient populations were based in The Netherlands and the US. As these studies with newer agents did not have a common comparator arm, the studies have been summarized separately.

Nuijten et al. [12] developed a Markov model to assess the cost effectiveness of the prokinetic agent prucalopride versus continued laxatives in patients with CC in The Netherlands, from a payer perspective. A description of continued laxatives was not reported, and neither was the definition of CC. The ICER for continued prucalopride treatment compared with laxatives was €9015 per QALY. The probabilistic sensitivity analysis indicated that there was a $>80\%$ probability that prucalopride is cost effective

Table 1 Overview of the methodology of the included studies

Study, year country	Population	Study characteristics	Strategies	Effectiveness data	Resource use/cost data	Funding source
Speed et al., 2010 [14] UK	People aged ≥ 55 years with chronic constipation, living in private households Prospective, pragmatic, three-armed cluster randomized trial with an economic evaluation (n = 145)	P = health service; T = 12 months; DR = NR; M = none; SA = NR	Laxatives Non-personalized dietary and lifestyle advice Personalized dietary and lifestyle advice, with reinforcement	Constipation-specific PAC-SYM and PAC-QOL measures, discomfort-free days Utility measured by EQ-5D	Personal Social Services Research Unit's unit costs of health and social care 2007: visits to a general practice, visits to hospital and telephone consultations between the start of the intervention, and at 3 months post-intervention	National Institute for Health Research Health Technology Assessment programme
Bub et al., 2006 US [18]	Nursing home residents with chronic constipation Double-blind, placebo-controlled, two-armed, parallel-group clinical trial (n = 86)	P = NR; T = 28 days; DR = NR; M = none; SA = NR	Placebo Herbal tea (smooth move)	Difference in total number of bowel movements (primary efficacy parameter), difference in average number of standard treatment dose dispenses	Cost assigned to the investigational product was derived from current wholesale distributor pricing Difference in total medication costs	Expenses related to the development of the study were assumed by the study sponsor
Lämås et al., 2010 Sweden [19]	Individuals with constipation as defined by the Rome II Criteria Non-blinded, randomized controlled trial conducted between January 2005 and March 2007 (n = 60)	P = direct healthcare costs; T = 9 weeks; DR = NR; M = none; SA = NR	Control: Continued using laxatives Intervention: Abdominal massage (self or professional)	HrQoL measured by EQ-5D at baseline, week 4, and week 8; VAS scale to calculate QALYs	Nursing time based on mean wages for enrolled nurses, nursing time and overhead costs from the hospital finance department, time spent on abdominal massage and travel from Statistics Sweden Societal perspective considered	Swedish Research Council, Ekchaga Foundation, The County Council of Vasterbotten, The Swedish Association of Health Professionals, and the Senior Centre of Vasterbotten
Taylor and Guest, 2009 UK [11]	Adults ≥ 18 years of age with chronic constipation History of constipation for 2 years or more before they received their first prescription	P = National Health Service; T = 6 months; DR = no discounting; M = decision tree; SA = PSA	Lactulose PEG 3350	Patients with chronic constipation in the THIN database Published utilities from the literature (general public using standard gamble)	Patients with chronic constipation in the THIN database (6-monthly number of clinician visits, hospital admissions, accident and emergency attendances, laboratory tests, diagnostic procedures and laxative prescriptions)	Norgine Pharmaceuticals Ltd

Table 1 continued

Study, year country	Population	Study characteristics	Strategies	Effectiveness data	Resource use/cost data	Funding source
Guest et al., 2008 UK [16]	Adults ≥ 18 years of age with chronic functional constipation	P = National Health Service; T = 3 months; DR = no discounting; M = decision tree; SA = PSA	Lactulose PEG 4000	Patients with chronic constipation in the THIN database Published utilities from the literature (general public using standard gamble)	Constipation-related resource use extracted from the THIN database (accident and emergency attendances, GP domiciliary visits, GP telephone consultations, GP visits in the clinic, hospital outpatient visits, laboratory tests, practice nurse visits)	NR
Christie et al., 2002 UK [17]	Idiopathic constipation in ambulant patients	P = National Health Service; T = 3 months; DR = no discounting; M = decision tree; SA = one-way	Lactulose PEG 3350 + electrolyte (PEG + E)	Previously reported single-blind, randomized, multicentre trial	Resource utilization estimates derived from a panel of six GPs and four nurses: GP consultations, district nurse domiciliary visits, outpatient visits to a gastroenterologist or colorectal surgeon, PEG + E and lactulose therapy, concomitant laxative medication and switched laxative therapy	Norgine Pharmaceuticals Ltd
Migeon-Duballet et al., 2006 France [20]	Severely intellectually and physically disabled residents of a mental health care, long-stay institution, who regularly suffered from constipation Retrospective study (before and after; *n* = 54/66)	P = NR; T = 21/24 months; DR = NR; M = none; SA = NR	PEG 3350 + electrolyte (one sachet every 3 days to a maximum of 3 sachets/day)	Clinical data for 21-month control period and 24-month treatment period Number of stools (primary efficacy variable), episodes of diarrhoea, body weights and blood chemistry	Monthly use and costs of laxatives, enemas and suppositories was obtained from hospital pharmacy records; the total hospital costs before and after introduction of PEG + E treatment was calculated	Unrestricted educational grant from Norgine Pharmaceuticals Ltd

Table 1 continued

Study, year country	Population	Study characteristics	Strategies	Effectiveness data	Resource use/cost data	Funding source
Passmore et al., 1993 UK [13]	Elderly patients with a history of chronic constipation in long-term hospital or nursing home care Double-blinded, randomized, crossover study (n = 77)	P = NR; T = two 14-day periods; DR = NR; M = none; SA = NR	Lactulose (15 ml twice daily) Senna–fibre combination (10 ml daily)	Stool frequency, stool consistency, and ease of evacuation; deviation from recommended dose, adverse effects	Total cost and cost per stool	NR
Nuijten et al., 2015 The Netherlands [12]	Chronic constipation in patients in The Netherlands in whom laxatives, over an extended period of time, did not provide adequate relief	P = Dutch payers; T = 1 year; DR = no discounting (3-year scenario analysis used 4% for economic outcomes and 1.5% for clinical outcomes); M = Markov model; SA = one-way and PSA	Continued laxative Prucalopride	Pooled information from published pivotal prucalopride clinical trials, national population statistics Utilities mapped to SF-6D and EQ-5D from constipation-specific PAC-SYM and PAC-QOL measures	Published Dutch price/tariff lists and Delphi panel for medication costs, management of chronic constipation, resource utilization associated with change of therapy after a failure and resulting from complications Indirect costs in a scenario analysis	NR
Huang et al., 2016 US [15]	Adult patients with chronic idiopathic constipation	P = payer; T = 4 weeks; DR = no discounting; M = decision tree; SA = one-way and PSA	Linaclotide (145 µg once daily) Lubiprostone (24 µg twice daily)	Clinical trial data (both published and post hoc analyses), published scientific literature, publicly available FDA reviews of lubiprostone Source of utility values NR	Survey of practicing physicians on resource utilization associated with treatment failure Indirect costs in a scenario analysis	Ironwood Pharmaceuticals and Forest Research Institute Inc., an Allergan affiliate

DR discount rate, *EQ-5D* EuroQol five-dimensions questionnaire, *GP* general practitioner, *HrQoL* health-related quality of life, *M* model, *NR* not reported, *P* perspective, *PAC-QOL* Patient Assessment of Constipation Quality of Life questionnaire, *PAC-SYM* Patient Assessment of Constipation Symptoms, *PSA* probabilistic sensitivity analyses, *QALYs* quality-adjusted life-years, *SA* sensitivity analyses, *SF-6D* Short-form six-dimension, *T* time horizon, *THIN* The health improvement network, *VAS* visual analogue scale

compared with continued laxative treatment, if the Dutch society was willing to pay at least €20,000 per QALY gained. Indirect costs of lost productivity were considered in a scenario analysis, which resulted in a decrease in the ICER to €5228 per QALY.

Using a decision-tree model from the US private payer perspective, Huang et al. [15] evaluated the agents linaclotide and lubiprostone in the treatment of adult patients with CC. The model population was adults diagnosed with chronic idiopathic constipation and candidates for prescription treatment. Compared with lubiprostone, linaclotide had lower per-patient costs and better response on the global assessment scale and in terms of spontaneous bowel movement (SBM) frequency. The model resulted in

Table 2 Overview of the outcomes of the included studies

Study, year Country	Treatment	Currency (year of value)	Total costs/ incremental costs	Effectiveness/incremental effectiveness	ICER	Authors' conclusions and limitations
Speed et al., 2010 UK [14]	(1) Laxatives (2) Personalized dietary and lifestyle advice, with reinforcement (3) Non-personalized dietary and lifestyle advice	British pound (2007/08)	Mean cost per case in each trial arm 1) £47.07 2) £33.69 3) £38.40	Differences in utility (EQ-5D) between control and intervention arms between baseline and 3 months 1) Referent 2) 0.02 3) 0.01 All trial arms experienced utility reduction	NR Results suggest dietary and lifestyle advice was less expensive, with similar differences in utility	Estimated savings in NHS costs are £13.34 for the personalized arm and £8.63 for the standardized arm Limitations: Due to the low number of participants in the trial, no firm conclusions could be drawn about the effectiveness of interventions
Bub et al., 2006 US [18]	(1) Placebo (2) Herbal tea (Smooth Move)	US dollar (NR)	Total costs in February (1) $429.04 (2) $278.05 Total costs in March (1) $458.01 (2) $256.42 Incremental: −$201.59	Statistically significant increase in the number of bowel movements in the Smooth Move group compared with placebo (average of 4.14 more bowel movements during the 28-day study period)	NR Results suggest herbal tea was dominant (less expensive and more effective)	Smooth Move, a traditional herbal tea formula for relieving constipation, has proven to be superior to placebo, as determined by a clinically relevant difference in the average number of bowel movements Limitations: tea given during day shift, while effects occurred on later shifts; other potentially related variables were not evaluated
Lämås et al., 2010 Sweden [19]	(1) Continued using laxatives (2) Abdominal massage (self or professional)	Euro (2008)	NR	(1) Mean HRQoL score reduction of 0.03 (0.70 to 0.67) (2) Mean HRQoL score gain of 0.06 (0.66 to 0.72)	Compared with control over 16 weeks: Self: €75,000 per QALY Professional: €60,000 per QALY	Abdominal massage statistically significantly increases HRQoL in people with constipation and may be a cost-effective treatment in the long term Limitations: No follow-up or blinding in trial; small sample size; data for self-massage based on massage from a massage therapist
Taylor and Guest, 2009 UK [11]	(1) Lactulose (2) PEG 3350	British pound (2007/08 prices)	Total 6-monthly NHS cost per patient (1) £419 (2) £420 Incremental: £1	Successfully treated within 6 months after starting treatment (1) 60% (2) 68% Health status at 6 months (1) 0.454 QALYs (2) 0.458 QALYs Incremental: 0.004 QALYs	1) Referent 2) £250 per QALY	Macrogol 3350 affords the NHS a cost-effective addition to the range of laxatives available for this potentially resource-intensive condition Limitations: Resource utilization not collected prospectively, significantly more macrogol 3350-treated patients received a prior laxative than lactulose-treated patients

Table 2 continued

Study, year Country	Treatment	Currency (year of value)	Total costs/ incremental costs	Effectiveness/incremental effectiveness	ICER	Authors' conclusions and limitations
Guest et al., 2008 UK [16]	(1) Lactulose (2) PEG 4000	British pound (2004/05 prices)	Total 3-monthly NHS cost per patient (1) £102 (2) £115 Incremental: £13	Successfully treated within 3 months after starting treatment (1) 31% (2) 42% Health status at 3 months (1) 0.210 QALYs (2) 0.213 QALYs Incremental: 0.003 QALYs	1) Referent 2) £4333 per QALY	Macrogol 4000 affords the NHS a cost-effective addition to the range of laxatives available for this potentially resource-intensive condition Limitations: Resource utilization not collected prospectively, successful treatment defined as discontinuing laxative treatment; other healthcare resources outside of the GP's surgery not included
Christie et al., 2002 UK [17]	(1) Lactulose (2) PEG + E	British pound (1999/2000 prices)	Total 3-monthly NHS cost per patient (1) £96 (2) £85 Incremental: −£11.10	Successful treatment at 3 months (1) 24% (2) 53% Incremental: 20%	PEG + E was dominant (less expensive and more effective)	PEG + E is a dominant treatment compared with lactulose Limitations: Resource utilization estimates based on expert opinion; study based on a controlled clinical trial; did not consider QoL improvements or patient preferences
Migeon-Duballet et al., 2006 France [20]	PEG 3350 + E (1) Before (2) After	Euros (1995–1998)	Total hospital medical ward expenditure per month (1) €3788 (2) €1767 Incremental: −€2021	Mean number of stools per patient per month (1) 12.4 (2) 24.9 Incremental: 12.5	NR Results suggest PEG 3350 + E may be cost effective	PEG + E in the management of constipation in people with severe intellectual disability may be cost effective, reducing hospital laxative costs Limitations: economic and efficacy/safety data collected did not directly correspond
Passmore et al., 1993 UK [13]	(1) Lactulose (2) Senna–fibre combination	British pound (NR)	Cost per stool (1) £39.70 (2) £10.30 Cost per treatment (1) £283.93 (2) £92.31 Incremental: −£191.62	Mean daily bowel frequency (1) 0.6 (2) 0.8 Incremental: 0.2	NR Results suggest senna–fibre combination was dominant (less expensive and more effective)	The senna–fibre combination was significantly more effective than lactulose at a lower cost Limitations: NR

Table 2 continued

Study, year Country	Treatment	Currency (year of value)	Total costs/ incremental costs	Effectiveness/incremental effectiveness	ICER	Authors' conclusions and limitations
Nuijten et al., 2015 The Netherlands [12]	(1) Continued laxative (2) Prucalopride	Euro (2011)	Total cost of treatment per patient (1) €2446 (2) €2511 Incremental: €65	QALYS (1) 0.826 (2) 0.833 Incremental: 0.007 QALYs	(1) Referent (2) €9015 per QALY	Prucalopride was cost effective in a Dutch patient population who had chronic constipation and who obtained inadequate relief from laxatives Limitations: Resource utilization based on the Delphi panel's estimates; placebo response as proxy for response to laxatives
Huang et al., 2016 US [15]	(1) Linaclotide (2) Lubiprostone	US dollar (2015)	Per-patient costs for response as global assessment (1) $946 (2) $1015 Incremental: $69 Per-patient costs for response as SBM frequency (1) $727 (2) $737 Incremental: $10	Treatment response rate based on global assessment of treatment (1) 39.3% (2) 35.0% Treatment response rate as SBM frequency (1) 58.6% (2) 59.6% QALYs per patient (1) 0.07 (2) 0.07 Incremental: 0 QALYs	Linaclotide was dominant (less expensive and more effective)	Linaclotide is less expensive with similar effectiveness when compared with lubiprostone for the treatment of CIC in adult patients Limitations: Short time horizon, direct costs based on survey; placebo-derived estimates of relative efficacy were derived; lack of data on lubiprostone

CIC chronic idiopathic constipation, *EQ-5D* EuroQol five-dimensions questionnaire, *GP* general practitioner, *HrQoL* health-related quality of life, *ICER* incremental cost-effectiveness ratio, *NHS* National Health Service, *NR* not reported, *PEG + E* PEG 3350 + electrolyte, *QALY* quality-adjusted life-year, *QoL* quality of life, *SBM* spontaneous bowel movement

equivalent QALYs per patient, with 0.07 QALYs for both lubiprostone and linaclotide. When indirect costs (i.e. the cost of lost work productivity) were included in the analysis, the authors noted the results were similar to those of the base-case results, however data were not reported in the study. Overall, authors concluded linaclotide was less expensive, with similar effectiveness, when compared with lubiprostone.

3.2.3 Laxatives ($n = 6$)

As described above, both non-pharmacological interventions were compared with unspecified laxatives. Six other economic evaluations evaluated either osmotic laxatives (PEG, lactulose) or stimulant laxatives (senna in combination with fibre).

3.2.3.1 Osmotic Laxatives

Four studies were identified that evaluated PEG, some of which included electrolytes, versus lactulose [11, 16, 17, 20]. Three of the four studies were based in the UK, with one study based in France. Two of the UK-based studies evaluated PEG for the treatment of adults with CC [11, 16]. Resulting ICERs for the comparison with lactulose were less than £4333 per QALY, with both studies using decision analytic modelling from the payer perspective. The authors of both studies concluded that PEG was a cost-effective addition to the range of laxatives available from the National Health Service (NHS). Another UK decision analytic modelling study evaluated PEG with electrolytes and compared this combination with lactulose from the payer perspective [17]. The patient population included those who had experienced at least one of the following two symptoms for at least 3 months: (1) fewer than three stools a week; or (2)

Table 3 Impact on cost effectiveness (studies reporting sensitivity analyses)

Impact on cost effectiveness	Model input parameters (also used in sensitivity analyses)	Study, year	Study countries
High/sensitive	Efficacy or treatment response	Nuijten et al., 2015 [12]	The Netherlands
	Probability of discontinuation of treatment		
	Probability of co-prescription of laxatives	Christie et al., 2002 [17]	UK
	Dosage of intervention treatment		US
	Number of additional GP consultations	Huang et al., 2016 [15]	
Moderate/ potentially sensitive	Probability of remaining on the initial laxative	Taylor et al., 2009 [11]	UK
	Switching to another laxative or adjunctive therapy		The Netherlands
	Dosage of concomitant laxative medication	Guest et al., 2008 [16]	
	Utility values (constipation, well controlled on medication)		
	Resource use (hospitalization, consultation specialist [GP or nurse])	Nuijten et al., 2015 [12]	
	Probability of having a follow-up test		
		Christie et al., 2002 [17]	
Low/insensitive	Drug price	Taylor et al., 2009 [11]	UK
	Dosage of treatment (control, switched laxative, concomitant laxative)		US
	Number of prescriptions (macrogol 4000 and lactulose)	Huang et al., 2016 [15]	
	Resource use (number of GP surgery visits, GP telephone consultations, nurse surgery visits, nurse domiciliary visits, hospital outpatient visits, accident and emergency attendances, laboratory tests)	Guest et al., 2008 [16]	
		Christie et al., 2002 [17]	

GP general practitioner

difficult evacuation. The authors found that PEG with electrolytes was the dominant strategy, with lower total 3-month costs per patient and a 20% greater successful treatment rate at 3 months [17]. In France, Migeon-Duballet et al. [20] also evaluated PEG with electrolytes by comparing data before and after its introduction in a retrospective study of a population of patients in a mental health care, long-stay institution who regularly suffered from constipation. The hospital perspective was considered. These results also suggested that the inclusion of PEG with electrolytes was dominant, with lower total hospital medical ward expenditure after introduction and a greater mean number of stools per patient per month compared with treatment with lactulose, phosphate enema and microenema.

3.2.3.2 Stimulant Laxatives Passmore et al. [13] assessed the efficacy and cost of a senna–fibre combination compared with lactulose in the treatment of CC in long-stay elderly patients in Northern Ireland and England. A history of CC was defined as fewer than three bowel movements a week. Compared with lactulose, the senna–fibre combination had lower costs, with a greater mean daily bowel frequency. The authors concluded that the senna–fibre combination was cost saving, i.e. more effective than lactulose at a lower cost.

In a US double-blind clinical trial of 86 nursing home residents with CC, a herbal tea combination with senna–fibre (Smooth Move) was compared with a placebo tea [18]. In a CCA, it was found that Smooth Move was less costly and resulted in a statistically significant increase in the number of bowel movements.

Overall, both PEG and senna–fibre combinations were found to be cost effective compared with lactulose, and, in some cases, cost-saving (lower costs and higher benefits); however, as reported in the previous sections, laxatives alone were not cost effective compared with diet advice and prucalopride.

3.3 Key Drivers of Cost Effectiveness

Key drivers of cost effectiveness identified in sensitivity analyses were categorized by their impact on the cost-effectiveness results, as identified by the study authors (Table 3). Overall, only half of the included studies performed sensitivity analyses to determine if the results of the models were robust to changes in input parameters. Trial analyses did not report conducting formal sensitivity analyses [13, 14, 18–20]. For studies that conducted sensitivity analyses, the authors concluded that sensitivity analyses showed stable cost-effectiveness results under input conditions varying from the base-case assumptions.

However, there were still some characteristics that affected the results of the cost-effectiveness models of treatment for CC more than others. Studies reported the highest sensitivity of cost effectiveness to efficacy or treatment response, which was most likely to be reported among newer agents. Sensitivity of the CEA to the probability of discontinuation or switching to another laxative was also categorized as high [12, 15, 17]. Parameters with a moderate impact on cost effectiveness included utility values and resource use such as hospitalization and specialist consultation [11, 12, 16, 17]. The impact of drug price, dosage of treatment, and number of prescriptions on cost effectiveness was low [11, 15–17]. Other resource use, i.e. number of GP surgery visits, GP telephone consultations, nurse surgery visits, nurse domiciliary visits, hospital outpatient visits, accident and emergency attendances and laboratory tests were also categorized as having a low effect on cost effectiveness.

3.4 Quality Assessment

A quality assessment of each of the studies using the CHEC list is shown in Table 4, while a description of the quality assessment and some important findings are reported below.

Although the quality assessment shows that the population was clearly described by each of the studies included, there were a number of differences in the definitions of CC. Some studies included patients with a diagnosis of CC (Rome II criteria, recorded diagnosis of functional constipation or chronic idiopathic constipation) [16, 17, 19]. In addition, some studies defined the patient population by select symptoms [12, 20], i.e. stool frequency (fewer than three stools a week or one stool or less in 48 h) or evacuation problems, while others defined the patient population by prescription [14, 18], i.e. those receiving laxatives (prescribed three or more times in the previous 12 months or used at least once a week) [13, 18].

The economic study design was found to be appropriate for all of the studies with respect to study objective. Designs included decision-tree models ($n = 4$) [11, 15–17], prospective trials ($n = 4$) [13, 14, 18, 19], a Markov model ($n = 1$) [12], and a regression analysis ($n = 1$) [20]. Incremental analysis of costs and outcomes of alternatives was performed in 6 of the 10 studies [11, 12, 15–17, 19]. Similarly, half of the studies subjected important variables to sensitivity analyses [11, 12, 15–17]. Of the 10 studies reviewed, 9 had a time horizon of 1 year or less, and thus, appropriately, did not discount both costs and benefits. One retrospective before and after study compared a 21-month before/control period and a

Table 4 Proportion of the included studies ($n = 10$) that answered 'yes' for each of the items of the CHEC list

CHEC questions	(%)
Q1. Is the study population clearly described?	100
Q2. Are competing alternatives clearly described?	90
Q3. Is a well-defined research question posed in answerable form?	100
Q4. Is the economic study design appropriate to the stated objective?	100
Q5. Is the chosen time horizon appropriate in order to include relevant costs and consequences?	70
Q6. Is the actual perspective chosen appropriate?	60
Q7. Are all important and relevant costs for each alternative identified?	40
Q8. Are all costs measured appropriately in physical units?	100
Q9. Are costs valued appropriately?	60
Q10. Are all important and relevant outcomes for each alternative identified?	90
Q11. Are all outcomes measured appropriately?	100
Q12. Are outcomes valued appropriately?	90
Q13. Is an incremental analysis of costs and outcomes of alternatives performed?	60
Q14. Are all future costs and outcomes discounted appropriately?	100
Q15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	50
Q16. Do the conclusions follow from the data reported?	100
Q17. Does the study discuss the generalizability of the results to other settings and patient/client groups?	60
Q18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	30
Q19. Are ethical and distributional issues discussed appropriately?	10

CHEC Consensus on Health Economic Criteria, *Q* question

24-month after/treatment period, but did not discuss discounting [20]. Another study incorporated a scenario analysis of a 3-year time horizon and discounted economic outcomes at 4% and clinical outcomes at 1.5% [12].

Sources of effectiveness and costing data varied; seven studies used clinical trial data [13–15, 17–20] (randomized controlled, pragmatic cluster randomized controlled), while other data came from published literature [12] and patient registries [11, 16]. Most studies (9 of 10) were considered to have used relevant outcomes and to have valued these outcomes appropriately. Only five studies reported QALYS [11, 12, 15, 16, 19] despite being recommended in many jurisdictions [21–24]. Health-related quality of life (HRQoL) was estimated from the general public using standard gamble [11, 16], EQ-5D [15], mapped to Short-Form Six-Dimension (SF-6D) and EQ-5D from constipation-specific measures (Patient Assessment of Constipation Symptoms [PAC-SYM] and Patient Assessment of Constipation Quality of Life questionnaire [PAC-QOL]) [12], or assessed using visual analogue scales [19]. Other outcome measures included successful treatment as measured by the discontinuation of laxative treatment [14], frequency of bowel movements [13, 17, 18, 20] and HRQoL [14].

Only six of the studies were considered to have valued costs appropriately [11–13, 15, 16, 19]. For costing data, a variety of sources were used: pharmaceutical formularies, healthcare professional wages, surveying healthcare providers, and local hospital/pharmacy departments. The majority of studies reported results from a payer perspective (NHS, Dutch payers, direct healthcare costs); however, all important and relevant costs for each treatment comparison were not considered in all studies. Specifically, for one trial-based economic evaluation, treatment costs only were considered; costs related to the management of CC with hospital admission, healthcare professional visits, laboratory tests, and diagnostic procedures were not incorporated [18].

Finally, only six studies discussed the generalizability of results to other settings/populations [11, 12, 15–17, 19], and even fewer indicated the absence of potential conflicts of interest (n = 3) [14, 19, 20]. Only one study discussed ethical and distributional issues [17].

4 Discussion

4.1 Summary of Evidence

Overall, 7 of the 10 included studies used trial data in their economic evaluations and incorporated costs from multiple sources. Varying definitions of CC were used to define the study population of interest. The majority of economic evaluations were not specific to one setting, however three studies evaluated treatments in a long-term hospital, nursing home, and mental health care institution setting [17, 19, 20]. Half of the studies reported QALYs as an outcome measure, while other measures included HRQoL, frequency of bowel movement, and laxative discontinuation. Nine of the 10 studies had time horizons of 1 year or less as their base-case, and the majority of studies considered only direct healthcare costs. Overall, there was considerable variation in the definition of CC and the source of costs used.

The evidence from 10 economic evaluations for the treatment of CC can be broadly categorized as two studies of non-pharmacological interventions compared with current treatment of laxatives, six evaluations where laxatives were the treatment of interest, and two studies of newer agents. Overall, when compared with current treatments (laxatives), there were additional benefits and cost savings with dietary and lifestyle advice, while abdominal massage was more effective and more costly [16, 18]. Compared with lactulose or current care, PEG with or without electrolytes was cost effective or cost saving, with lower costs and improved health benefits, while a senna–fibre combination compared with lactulose was also cost saving [11, 13, 16–18, 20]. For newer agents, compared with laxatives, prucalopride was considered cost effective at €9015/QALY gained [12]. Two newer agents were also compared, and results suggested linaclotide had greater SBMs at cost savings than lubiprostone [15]; however, equivalent QALYs were gained with both agents [15].

Overall, results from the summary of economic evaluations for the treatment of CC align with current practice guidelines [1, 8]. Specifically, evidence supports recommendations to provide dietary/lifestyle modifications in addition to laxatives or an alternative approach to current care. Among laxatives, evidence suggests that PEG with or without electrolytes, as well as the senna–fibre combination, are effective and cost effective compared with lactulose, although no study has compared all available laxative treatments. For those patients who have insufficient relief while taking laxatives, there is some evidence that prucalopride is preferred when compared with continued lactulose, and linaclotide is preferred to lubiprostone, although no study has compared all available options, i.e. continued laxatives, prucalopride, linaclotide and lubiprostone. These results support current guidelines that recommend these newer agents following treatment with laxatives.

4.2 Critique of the Evidence

As discussed in the Results section, there are many methodological differences in the studies reviewed. Time horizons range from 28 days to 2 years. While five studies

reported QALYs, many studies used other clinical measures. Those studies that did report QALYs used a number of different techniques for estimating the health state utility scores. Different types of costs were included in each analysis and patient populations were defined in many different ways.

It is recommended that the time horizon of an economic evaluation be sufficiently long enough to capture all of the costs and benefits of the intervention [22, 25]. Since there are no expected mortality effects of CC interventions, using a time horizon shorter than a lifetime model is justified. It is unlikely that 28 days will be sufficiently long to capture the consequences of these interventions, particularly since discontinuation and switching treatments have been found to be important to the cost-effectiveness results.

Ideally, economic evaluations should report the QALY to improve comparisons between studies and to allow decision makers to compare across diseases [22–25]. As almost all effectiveness outcomes were estimated using clinical trial data, more studies using real-world data would also be useful to validate trial-based economic evaluations.

One study reported only treatment costs [18], which is insufficient to meet economic evaluation criteria as many other costs are relevant, even from the more limited payer perspective. The analysis of key drivers of cost effectiveness suggests that, in particular, hospitalization and specialist consultation costs have an important impact. Furthermore, literature suggests that in addition to higher direct costs of healthcare resources, patients with CC report significantly lower levels of work productivity, and higher absenteeism and overall work impairment compared with matched controls [21]. However, few studies reported results from the societal perspective [12, 15, 19].

As mentioned previously, the definition of the patient populations varied significantly. This makes comparisons across studies difficult. It is recommended that economic evaluations use common definitions of constipation, such as the Rome III criteria. Additionally, to be able to place patients within the current recommendations of step therapy, patient populations should be defined by symptoms despite use of their current treatments. This was done well in an economic evaluation of a newer treatment which specified patient populations that had symptoms despite their use of laxatives [12]. CC primarily affects patients of advanced age, which was reflective of patient populations in the included studies; however, constipation is also common in childhood and many children require medical treatment and nursing care [22]. None of the included studies evaluated idiopathic childhood constipation. Furthermore, other patient subpopulations (i.e. those with spinal cord injury) were also not specifically analysed.

The studies included in this review were published over a period of 23 years (1993–2016) and almost all studies were conducted in Europe, with five from the UK [11, 14, 15, 17, 18], one from France [19], one from The Netherlands [12] and one from Sweden [16]. An additional two studies were conducted in the US [13, 20]. There are a limited number of economic evaluations for treatments of CC overall and by country; no country had assessments of all treatments or an assessment of the recommended step therapy. Half of the studies were based in the UK but focused primarily on treatment with PEG. There were no comparisons of newer agents to laxatives; however, these may not be needed if newer agents are only recommended for use in populations of severe CC for patients who have already not responded to laxatives [8].

The impact of the funding source on economic evaluation results is unknown. Positive results were noted for all studies funded by the manufacturer of the treatment under comparison; however, not all studies reported the funding source. It is recommended that all funding sources and conflicts of interest be reported and that, where possible, conflicts of interest should be avoided [26]. Recently, there has been more interest in the distributional and equity effects of recommending new treatments [27]. Generally, a health benefit is considered of equal value regardless of other characteristics of the individuals, such as their sociodemographic characteristics, age, or level of health. It is recommended that authors discuss potential advantages or disadvantages that could be experienced by any groups due to the implementation of new treatments, particularly those groups with characteristics protected by the government.

4.3 Strengths and Limitations

To our knowledge, this is the first study to systematically review the cost-effectiveness literature on available treatments for CC. Several databases were searched and these databases included the vast majority of health economics publications. Furthermore, a validated and internationally accepted quality assessment tool (CHEC list) was used to assess the quality of economic evaluations of treatment for CC.

With respect to limitations, some relevant studies may have been overlooked in our review, especially those that were not published in the English language. Furthermore, partial economic evaluations, cost-of-illness studies, CMAs, and cost-benefit analyses were excluded. In addition, we did not formally assess potential publication bias that may have occurred due to the lack of inclusion of unpublished studies (e.g. industry-sponsored evaluations), which may have had unfavourable findings. Evidence synthesis was not possible given the differences in the study populations, comparators and outcomes.

5 Conclusions

The definition of CC, and thus study population, in the included economic evaluations vary and many different outcomes have been reported. Consistency in the definition of CC and the use of QALYs is recommended. There is no evaluation that includes all comparators of laxatives, and neither is there an evaluation that includes all available treatments for those patients who have not responded to treatment with laxatives. Overall, results from economic evaluations appear to align with current practice evidence guidelines of following a stepwise approach to treatment for CC.

Data Availability Statement All data generated or analysed during this study are included in this published article (and its supplementary information files).

Author Contribution DH, FC, DL and ES designed the search strategy and study protocol. DH and NI reviewed all abstracts and papers, were responsible for the data abstraction, undertook the quality assessment and prepared the figures and tables. DH and ES drafted the manuscript, and all authors reviewed and approved the final version for publication.

Compliance with Ethical Standards

Conflict of interest Dolly Han, Nicolas Iragorri, Fiona Clement, Diane Lorenzetti and Eldon Spackman report no conflicts of interest.

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