Controlling faecal incontinence in women by performing anal exercises with biofeedback or loperamide: a randomised clinical trial

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Summary

Background Well designed, large comparative effectiveness trials assessing the efficacy of primary interventions for faecal incontinence are few in number. The objectives of this study were to compare different combinations of anorectal manometry-assisted biofeedback, loperamide, education, and oral placebo.

Methods In this randomised factorial trial, participants were recruited from eight clinical sites in the USA. Women with at least one episode of faecal incontinence per month in the past 3 months were randomly assigned 0·5:1:1:1 to one of four groups: oral placebo plus education only, placebo plus anorectal manometry-assisted biofeedback, loperamide plus education only, and loperamide plus anorectal manometry-assisted biofeedback. Participants received 2 mg per day of loperamide or oral placebo with the option of dose escalation or reduction. Women assigned to biofeedback received six visits, including strength and sensory biofeedback training. All participants received a standardised faecal incontinence patient education pamphlet and were followed for 24 weeks after starting treatment. The primary endpoint was change in St Mark's (Vaizey) faecal incontinence severity score between baseline and 24 weeks, analysed by intention-to-treat using general linear mixed modelling. Investigators, interviewers, and outcome evaluators were masked to biofeedback assignment. Participants and all study staff other than the research pharmacist were masked to medication assignment. Randomisation took place within the electronic data capture system, was stratified by site using randomly permuted blocks (block size 7), and the sizes of the blocks and the allocation sequence were known only to the data coordinating centre. This trial is registered with ClinicalTrials.gov, number NCT02008565.

Findings Between April 1, 2014, and Sept 30, 2015, 377 women were enrolled, of whom 300 were randomly assigned to placebo plus education (n=42), placebo plus biofeedback (n=84), loperamide plus education (n=88), and the combined intervention of loperamide plus biofeedback (n=86). At 24 weeks, there were no differences between loperamide versus placebo (model estimated score change –1·5 points, 95% CI –3·4 to 0·4, p=0·12), biofeedback versus education (–0·7 points, –2·6 to 1·2, p=0·47), and loperamide and biofeedback versus placebo and biofeedback (–1·9 points, –4·1 to 0·3, p=0·092) or versus loperamide plus education (–1·1 points, –3·4 to 1·1, p=0·33). Constipation was the most common grade 3 or higher adverse event and was reported by two (2%) of 86 participants in the loperamide and biofeedback group and two (2%) of 88 in the loperamide plus education group. The percentage of participants with any serious adverse events did not differ between the treatment groups. Only one serious adverse event was considered related to treatment (small bowel obstruction in the placebo and biofeedback group).

Interpretation In women with normal stool consistency and faecal incontinence bothersome enough to seek treatment, we were unable to find evidence against the null hypotheses that loperamide is equivalent to placebo, that anal exercises with biofeedback is equivalent to an educational pamphlet, and that loperamide and biofeedback are equivalent to oral placebo and biofeedback or loperamide plus an educational pamphlet. Because these are common first-line treatments for faecal incontinence, clinicians could consider combining loperamide, anal manometry-assisted biofeedback, and a standard educational pamphlet, but this is likely to result in only negligible improvement over individual therapies and patients should be counselled regarding possible constipation.

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Introduction

Faecal incontinence, also known as accidental bowel leakage, is the involuntary leakage of stool, including liquid or solid faeces or mucus. It is a chronic, debilitating condition that has a substantial effect on quality of life[1] and is common in community-dwelling adults,[2] with prevalence estimates ranging from 2% to 21%.[3] The economic burden is high, and adults with faecal

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Research in context

Evidence before this study

Loperamide is a synthetic opioid receptor agonist that is commonly used to treat diarrhoea. Although anti-diarrhoeal medications are superior to placebo in the treatment of patients with diarrhoea-associated faecal incontinence, little evidence supports its use for faecal incontinence in those without extremes of stool consistency. Anorectal manometry-assisted biofeedback treats faecal incontinence by targeting anal sphincter muscle strength and response to rectal sensations, although the efficacy is not known. It is also time-consuming, expensive, and requires specialised expertise from the therapist and an ongoing commitment from the patient. Well designed, large comparative effectiveness trials assessing the efficacy of primary interventions for faecal incontinence are few in number. Data for the literature search were identified by searches of Cochrane Library, PubMed, and ClinicalTrials.gov, recommendations from the National Institutes of Health State of the Science Consensus Conference on Prevention of urinary and faecal incontinence (2008), and references from relevant articles using the search terms "clinical trials", "loperamide", "biofeedback", "manometry-assistance", "faecal incontinence", "quality of life", "outcomes", "minimum import difference", "responsiveness", "constipation", and "adherence". Only articles published in English from Jan 1, 1950, to Dec 31, 2010, were reviewed.

Added value of this study

This trial studied the effect of loperamide and anal muscle exercises with biofeedback compared with oral placebo and an educational pamphlet in women with faecal incontinence. It also compared the effect of combination therapy to each individual therapy. At 24 weeks, there were no differences between loperamide versus oral placebo, biofeedback versus education, loperamide and biofeedback versus oral placebo, and biofeedback versus loperamide plus education.

Implications of all the available evidence

In women with normal stool consistency and faecal incontinence that was bothersome enough to seek treatment, we were unable to find evidence against the null hypotheses that loperamide is equivalent to placebo, that anal exercises with biofeedback is equivalent to an educational pamphlet, and that loperamide and biofeedback together are equivalent to oral placebo and biofeedback or loperamide plus an educational pamphlet. Because these interventions are common first-line treatments for faecal incontinence, clinicians could consider combining loperamide, anal manometry-assisted biofeedback, and a standard educational pamphlet, but this is likely to result in only negligible improvement over individual therapies and patients should be counselled regarding possible constipation from loperamide.

incontinence can have substantially higher annual health-care costs than do those without.[4] Faecal incontinence is multifactorial in nature and can result from impaired anal sphincter muscle strength, decreased rectal sensation, loss of urgency control, and altered stool consistency.

Loperamide is a synthetic opioid receptor agonist, commonly used to treat diarrhoea.[5] Loperamide works primarily by slowing whole-gut transit time and decreasing stool weight,[6] theoretically increasing stool firmness, making it easier for the rectum to store and evacuate faeces. Loperamide might have a role in treatment of patients with normal transit, because it also affects rectal or anal sphincter function by increasing rectal perception and volume of leaked stool, increasing squeeze duration and decreasing faecal urgency.[7] Although anti-diarrhoeal medications such as loperamide are superior to placebo in the treatment of patients with diarrhoea-associated faecal incontinence, evidence to support their use for faecal incontinence in those without extremes of stool consistency is based on trials with small sample sizes and little follow-up.[8,9]

Anorectal manometry-assisted biofeedback treats faecal incontinence by targeting anal sphincter muscle strength and the response to rectal sensations, although the actual efficacy is not known.[10] Anorectal manometry-assisted biofeedback is time-consuming and expensive and requires specialised expertise from the therapist and an ongoing commitment from the patient.

Well designed, comparative effectiveness trials assessing the efficacy of primary interventions for faecal incontinence are few in number. The primary aims of the Controlling Anal incontinence by Performing Anal Exercises with Biofeedback or Loperamide (CAPABLe) trial were to compare the change from baseline in St Marks (Vaizey) score at 24 weeks after treatment initiation between women randomly assigned to loperamide or oral placebo and anal sphincter exercises with biofeedback or usual care using a standardised educational pamphlet and to compare the two active treatments combined or alone.

Methods

Study design

The CAPABLe trial was a randomised factorial trial done between April 2, 2014, and June 13, 2016, at eight academic medical centres in the USA participating in the Eunice Kennedy Shriver National Institute of Child Health and Human Development sponsored Pelvic Floor Disorders Network. The detailed study design has been published.[11] Women who reported having any uncontrolled loss of liquid or solid faecal material that occurred at least monthly over the past 3 months and was bothersome enough to seek treatment

and who had negative colon cancer screening were invited to participate.[12] Women who reported their typical bowel movement over the past 3 months as type 1 (hard) or type 7 (watery) using the Bristol Stool Form were excluded.[13] Women who had received previous abdominal or pelvic floor radiation were excluded. A detailed list of the inclusion and exclusion criteria is available in the appendix (p 1). All study sites received institutional review board approval and all participants gave written informed consent.

Randomisation and masking

Enrolled participants underwent a single randomisation using a 0·5:1:1:1 allocation to one of four treatment combinations: oral placebo plus education, oral loperamide plus education, oral placebo plus anal sphincter exercise training using manometry-assisted biofeedback, and oral loperamide plus anal sphincter exercise training using manometry-assisted biofeedback. Fewer patients were assigned to the combination of placebo drug and usual care (educational pamphlet) to minimise the potential burden on the minimal intervention group. Randomisation was stratified by site using randomly permuted blocks (block size 7). Blocks were generated using random sampling without replacement, where each block contained all possible treatments in the appropriate allocation ratios. A sufficient number of blocks was generated for each site to allow for maximum allowable site enrolment and provide extra randomisations to account for errors. Site enrolment was not allowed to exceed 25% of the total sample size (73 participants). To form the sequence of randomisations, the order of blocks in each site was randomly permuted. The randomisation sequence was then administered within the electronic data capture system. Block sizes and randomisation sequences were known only to the data coordinating centre.

Throughout the study, investigators, interviewers, and outcome evaluators were masked to treatment assignment for the biofeedback intervention. Participants and all study staff other than the research pharmacist were masked to the medication assignment. Loperamide and placebo were masked through overencapsulation by standard DB Capsules (Capsugel, Morristown, NJ, USA). Overencapsulation, bottling, and labelling were done by a qualified contract manufacturing organisation and drug supply was provided to each site. Two-part labels were used and a placebo tablet was manufactured to match the loperamide tablet as closely as possible in appearance and weight. A standard inert excipient (Avicel) was used to backfill the overencapsulated active drug and placebo tablet.

After initial screening, eligible patients were given a bowel diary that they filled out for 7 days consecutively and received a quality-of-life telephone interview from by the data coordinating center. Randomisation, review of bowel diary, and diagnostic anorectal manometry were done at the baseline visit 2–4 weeks after screening. Participants not assigned to biofeedback had baseline and 12 and 24 week visits. Participants assigned to biofeedback had visits at baseline and 2, 4, 6, 9, 12, and 24 weeks.

Procedures

Participants assigned to the biofeedback group received an individualised programme that included diagnostic anorectal manometry evaluation, biofeedback strength training, and sensory or urge resistance training (mcompass; Medspira, Minneapolis, MN, USA). Participants who received biofeedback were prescribed a home exercise programme based on their individual performance during the intervention visits. All study interventionists underwent standardised training.[14]

See Online for appendix

Participants initially received placebo or 2 mg of oral loperamide (one capsule) per day (time of day was not specified) with the option of dose escalation up to a maximum of four capsules daily and the option of dose reduction owing to adverse effects to one capsule every other day. Dose escalation, maintenance, or reduction was recommended to participants by telephone or during in-person visits with study coordinators on the basis of balancing efficacy and side-effects of treatment using two Likert scales: the Patient Global Symptom Control rating scale[15] ("My current treatment is giving me adequate control of my stool leakage") and the Patient Global Tolerability rating Scale, which was modified using the Patient Global Symptom Control scale ("My current medication is giving me bothersome side effects"). Responses on both scales ranged from 1, disagree strongly, to 5, agree strongly. Participants reporting inadequate control of stool leakage and bothersome side-effects were instructed to discontinue the study medication but were asked to remain in follow-up, if possible, until follow-up was complete, they formally withdrew, or became lost to follow-up. Participants reporting deterioration in faecal incontinence symptoms after discontinuing study drug owing to side-effects were allowed to restart the study drug after an assessment and decision by the site investigator.

Education consisted of providing the participant a publicly available pamphlet[16] from the National Institute of Diabetes and Digestive and Kidney Diseases with deletion of a single reference to loperamide. The pamphlet discusses symptoms, causes, diagnosis, and treatments—including dietary treatment—for bowel control problems, and it was provided to all participants. The pamphlet was provided to all participants because basic educational materials were widely available on the internet and through other sources. Provision of a standardised, peer-reviewed, publicly available educational pamphlet ensured all participants at least received similar minimum basic educational information.

Outcomes

On the basis of National Institutes of Health consensus recommendations,[17] trials in faecal incontinence should use a primary outcome measure that incorporates a patient

perspective, faecal incontinence frequency, severity, bother, and desire for treatment. For this study, the primary outcome measure that investigators felt incorporated these properties and whose psychometric properties were measured was the change from baseline to 24 weeks in the St Mark's (Vaizey) faecal incontinence severity scale.[18,19] Data on the primary outcome were continually reviewed by the data safety and monitoring board throughout the study. For follow-up visits, the medication item on this scale was modified to "taking constipating medicines other than the study medicine", because all participants were assigned to take either loperamide or placebo.

Secondary outcomes included leakage episodes and pad use as measured by a 7-day diary, quality-of-life scores as measured by Colorectal-Anal Distress Inventory (CRADI) subscale on the Pelvic Floor Distress Inventory (range 0 [least impact] to 100 [most impact], minimum important difference –5),[20,21] Colorectal-Anal Impact Questionnaire (CRAIQ) subscale on the Pelvic Floor Impact Questionnaire (range 0 [least impact] to 100 [most impact], minimum important difference –8),[20,21] and the Modified Manchester Health Questionnaire (MMHQ) severity subscale (range 0 [least impact] to 100 [most impact], minimum important difference –3),[20,22] modified Patient Global Impression of Improvement (PGI-I) scale for bowel function,[23] anal sphincter tone on physical examination using the digital rectal examination scoring system,[24] and anal manometry measures. Dietary fibre intake was measured using the Fruits/Vegetables/Fiber Screener questionnaire.[25] Adherence was measured using pill counts, a provider-reported adherence question,[26] and modified Medication Adherence Self-Report Inventory.[27] Outcomes not reported here included the Fecal Incontinence Adaptation Index,[28] Medical Outcome Study Short-Form-12,[29] body image as measured by the Body Image Scale,[30,31] Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire extended version,[32,33] a new Accidental Bowel Leakage instrument, Patient Assessment of Constipation Symptoms questionnaire,[34] and productivity loss, including days of missed work, missed household chores, caregiver costs, travel time, transportation costs, out-of-pocket appointment costs, incontinence products costs, and laundry costs. These outcomes will be reported separately. Quality-of-life measures were done by telephone interview any time between the screening and baseline visits and again at 12 and 24 weeks. Serious and non-serious adverse events were collected and reported to the data safety and monitoring board.

Statistical analysis

The study was powered to detect a minimally important difference of –5 points for the change from baseline in St Mark's score (appendix p 1).[18] A sample size of 245, with 35 participants in the placebo plus education group and 70 in each of the other three groups, provided 90% power to detect at least a 5-point marginal difference in each treatment group at a 0·025 level of significance, assuming a standard deviation of 8·5. This sample size also provided 55% power to detect a difference in combined drug and exercise versus either intervention alone, at a 0·05 level of significance, conservatively assuming a modest negative interaction. Projecting a conservative follow-up of 85% of participants at 24 weeks, the sample size was set at 294 patients (42 in the placebo plus education group and 84 in each of the other groups).

The change from baseline in St Mark's score at 24 weeks was analysed by use of a general linear mixed model with treatment assignments, interaction between drug and exercise, week (12 or 24), interactions between week and treatment, Rome III irritable bowel syndrome clinical trial status[34] and its interaction with treatment, and clinical site as independent variables. The model accounted for the dependence between repeated measurements on the same participant by modelling the within-participant covariance structure. Participants with outcomes assessed at one or both post-treatment time points (12 and 24 weeks) were included in the statistical models. Two-sided tests of the marginal effects of medication and biofeedback treatment assignments at 24 weeks were done at a type I error level of 0·025. Combination treatment was compared with each of medication (loperamide) or biofeedback alone at a type I error level of 0·05.

Second ary outcomes were evaluated similarly. For categorical outcomes, generalised linear mixed modelling with a logit link was used. For the anal manometry measures, the actual manometry values assessed at 12 and 24 weeks were analysed rather than changes from baseline, because investigators believed changes in values were less clinically interpretable. Analysis of adverse events compared the proportion of participants with reported events between the four treatment combinations using χ^2 tests.

Primary and secondary outcomes were analysed using intention-to-treat, with the limitation that only observed outcomes at 12 and 24 weeks were included in analysis. A sensitivity analysis of the primary outcome was done using multiple imputation to assess the effects of model assumptions regarding missing data. Per-protocol analysis of participants who adhered to their assigned treatment was also done, because treatment adherence has been shown to explain variation in biofeedback effect for women with faecal incontinence.[35] Adherence in the study drug group was defined as participants who reported at 12 and 24 weeks that they took some study drug in the past 3 days. However, participants assigned to placebo who reported taking loperamide were excluded. Adherence to biofeedback was defined as attending at least five of six intervention sessions and reporting at 12 and 24 weeks that at least one set of exercises was done on at least 2 of the past 3 days. For both drug and biofeedback, women who were adherent at 12 weeks had data for that time point included in the analysis even if they were non-adherent at 24 weeks. The

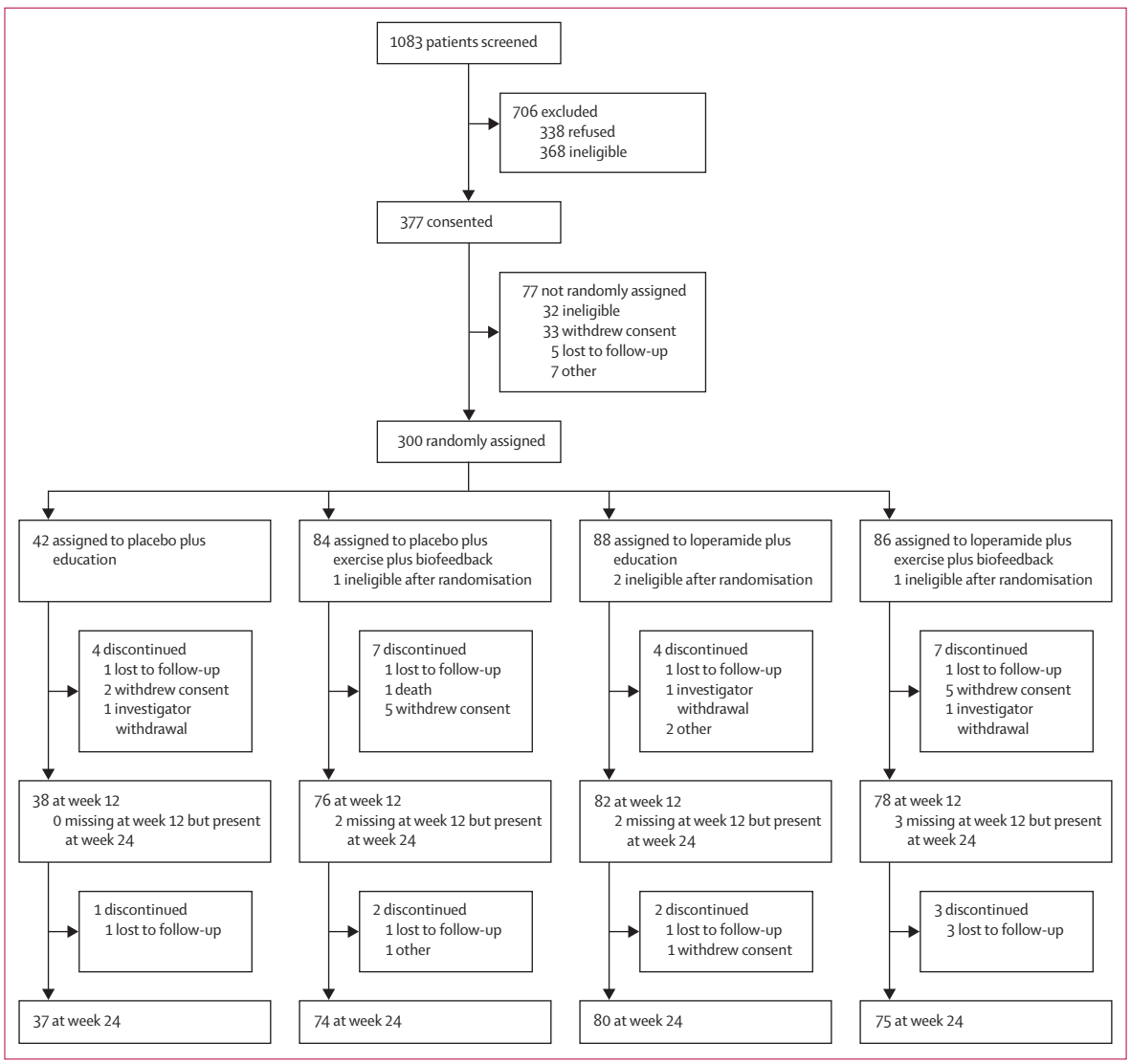

Figure: **Study profile**

methods used in the intention-to-treat analyses were repeated for the per-protocol population. Adverse events were compared between participants included in the per-protocol analysis and those who were excluded. No adjustments were made for multiple statistical testing, and comparisons of secondary outcomes were considered exploratory. All analyses were done using SAS version 9.4. An independent data safety and monitoring board reviewed the progress and safety of the study. This trial is registered with ClinicalTrials.gov, number NCT02008565.

Role of the funding source

An author (SFM) from the sponsor, National Institute of Child Health and Human Development, assisted in the literature search, figures, study design, data collection, data analysis, data interpretation, and writing of the manuscript. No industry funding or provision of medications was received. The authors have not been paid to write this article by a pharmaceutical or medical device company or other agency. Pelvic Floor Disorders Network (PFDN) Equipment was purchased at or below cost from Medspira by Research Triangle Institute on behalf of the PFDN in return for PFDN providing consultation on mcompass biofeedback software modifications, for which MGG (senior statistician) was responsible. Medspira had no input into the design, implementation, data collection, or analysis of this trial. BC had access to the raw data during the study. JEJ had final responsibility to submit for publication.

Results

We enrolled 377 women between April 1, 2014, and Sept 30, 2015 (figure). Of the women who consented,

	Loperamide (N=171)	Placebo (N=125)	Exercise plus biofeedback (N=168)	Education only (N=128)
Age, median (IQR)	64·4 (58·1–71·4)	63·3 (56·1–71·4)	64·5 (58·3–72·2)	64·0 (56·4–70·0)
Race, n (%)				
Native American or Alaskan	1 (<1%)	2 (2%)	1 (<1%)	2 (2%)
Black or African American	26 (15%)	20 (16%)	26 (15%)	20 (16%)
More than one race	4 (2%)	1 (<1%)	5 (3%)	0 (0%)
Other	4 (2%)	4 (3%)	4 (2%)	4 (3%)
White	136 (80%)	98 (78%)	132 (79%)	102 (80%)
Ethnicity, n (%)				
Hispanic or Latina	15 (9%)	11 (9%)	16 (10%)	10 (8%)
Not Hispanic or Latina	154 (90%)	111 (89%)	149 (89%)	116 (91%)
Unknown or not reported	2 (1%)	3 (2%)	3 (2%)	2 (2%)
Insurance, n (%)				
Private or health maintenance organisation	100 (58%)	81 (65%)	105 (63%)	76 (59%)
Medicaid or Medicare	99 (58%)	59 (47%)	89 (53%)	69 (54%)
Self-pay	1 (<1%)	3 (2%)	3 (2%)	1 (<1%)
Other	12 (7%)	10 (8%)	13 (8%)	9 (7%)
Vaginal deliveries, median (range)	2·0 (0·0–7·0)	2·0 (0·0–7·0)	2·0 (0·0–7·0)	2·0 (0·0–7·0)
Caesarean deliveries, median (range)	0·0 (0·0–4·0)	0·0 (0·0–5·0)	0·0 (0·0–5·0)	0·0 (0·0–2·0)
Menstrual status, n (%)				
Not sure	7 (4%)	9 (7·2%)	9 (5%)	7 (5%)
Post-menopausal	148 (87%)	103 (82%)	143 (85%)	108 (84%)
Pre-menopausal	16 (9%)	13 (10%)	16 (10%)	13 (10%)
Currently using oestrogen therapy, n (%)				
Oral/Patch	17 (10%)	11 (9%)	15 (9%)	13 (10%)
Vaginal	43 (25%)	32 (26%)	46 (27%)	29 (23%)
Current smoker, n (%)	11 (6%)	10 (8%)	11 (7%)	10 (8%)
Connective tissue disease	6 (4%)	6 (5%)	8 (5%)	4 (3%)
Previous accidental bowel leakage surgery	7 (4%)	6 (5%)	9 (5%)	4 (3%)
Previous rectal or anal surgery	22 (13%)	18 (15%)	24 (14%)	16 (13%)
Previous hysterectomy	90 (53%)	58 (46%)	85 (51%)	63 (49%)
Previous urinary incontinence surgery	44 (26%)	33 (26%)	46 (27%)	31 (24%)
Previous pelvic organ prolapse surgery	40 (23%)	30 (24%)	44 (26%)	26 (20%)
Body-mass index, kg/m²	30·5 (7·0, 17·5–56·8)	29·2 (8·1, 17·1–67·5)	29·3 (7·1, (17·1–56·8)	30·8 (8·0, (20·2–67·5)
Dietary fibre score	15·8 (6·5, 4·0–41·0)	15·7 (6·1, 2·0–33·0)	16·3 (6·2, 4·0–41·0)	15·1 (6·5, (2·0–33·0)
Daily fibre intake, grams	15·1 (4·8, 6·4–33·7)	15·0 (4·5, 4·9–27·8)	15·4 (4·6, 6·4–33·7)	14·6 (4·8, 4·9–27·8)
Bristol stool scale				
Type 2	25 (15%)	20 (16%)	27 (16%)	18 (14%)
Type 3	29 (17%)	14 (11%)	23 (14%)	20 (16%)
Type 4	50 (29%)	43 (34%)	49 (29%)	44 (34%)
Type 5	31 (18%)	22 (18%)	34 (20%)	19 (15%)
Type 6	36 (21%)	26 (21%)	35 (21%)	27 (21%)
Rome III irritable bowel syndrome clinical status	32 (19%)	24 (19%)	34 (20%)	22 (17%)
Rome III irritable bowel syndrome diagnostic status	75 (44%)	49 (40%)	69 (41%)	55 (43%)
Number of accident-free days	2·8 (2·2)	3·0 (2·1)	3·0 (2·2)	2·8 (2·1)
Number of pad-change leaks per week	4·3 (6·7)	4·4 (6·3)	4·3 (6·6)	4·4 (6·4)
Number of leaks per day	1·7 (1·8)	1·5 (1·8)	1·6 (1·8)	1·6 (1·7)

Values are n (%), median (IQR), mean (SD, range), or mean (SD).

Table 1: **Baseline clinical and demographic characteristics of randomly assigned and eligible participants**

300 were randomly assigned to placebo plus education (n=42), placebo plus biofeedback (n=84), loperamide plus education (n=88), and the combined intervention of loperamide plus biofeedback (n=86). Similar numbers of withdrawals occurred after randomisation among groups. Four participants were ineligible after randomisation (one

	Loperamide			Placebo			Model-estimated difference (95% CI)	Exercise plus biofeedback			Education only			Model-estimated difference (95% CI)
	N	Mean (SD)	Mean change from baseline (95% CI)	N	Mean (SD)	Mean change from baseline (95% CI)		N	Mean (SD)	Mean change from baseline (95% CI)	N	Mean (SD)	Mean change from baseline (95% CI)	
St Mark's (Vaizey) score														
Week 0	160	14·2 (4·2)	..	114	14·2 (3·9)	..	..	154	14·2 (4·1)	..	120	14·1 (4·0)	..	..
Week 24	155	8·3 (5·5)	−6·2 (−7·4 to −5·0)	111	9·3 (5·3)	−4·7 (−6·2 to −3·1)	−1·5 (−3·4 to 0·4); p=0·12	149	8·4 (5·3)	−5·8 (−7·0 to −4·6)	117	9·1 (5·6)	−5·1 (−6·6 to −3·6)	−0·7 (−2·6 to 1·2); p=0·47
CRADI score														
Week 0	160	49·7 (22·7)	..	114	50·0 (19·8)	..	..	154	49·2 (20·9)	..	120	50·6 (22·3)	..	..
Week 24	146	30·2 (23·2)	−21·6 (−25·9 to −17·3)	105	31·5 (21·0)	−15·7 (−21·5 to −9·9)	−5·9 (−13·0 to 1·1); p=0·096	142	31·5 (21·0)	−18·6 (−23·0 to −14·1)	109	33·7 (22·9)	−18·7 (−24·4 to −13·0)	0·1 (−7·0 to 7·2); p=0·97
CRAIQ score														
Week 0	160	43·6 (28·5)	..	114	40·6 (27·6)	..	..	154	41·4 (27·4)	..	120	43·5 (29·0)	..	..
Week 24	143	26·1 (27·5)	−17·5 (−21·8 to −13·2)	104	29·3 (27·1)	−14·9 (−20·6 to −9·2)	−2·6 (−9·5 to 4·3); p=0·46	141	27·3 (28·3)	−14·4 (−18·8 to −10·1)	106	27·6 (26·2)	−18·0 (−23·6 to −12·4)	3·6 (−3·4 to 10·5); p=0·31
Number of accident-free days														
Week 0	159	2·8 (2·2)	..	112	3·0 (2·1)	..	..	153	3·0 (2·2)	..	118	2·8 (2·1)	..	..
Week 24	149	4·8 (2·3)	2·1 (1·6 to 2·6)	107	4·9 (2·3)	2·0 (1·3 to 2·7)	0·1 (−0·7 to 0·9); p=0·80	143	5·3 (2·1)	2·2 (1·7 to 2·7)	113	4·3 (2·4)	1·9 (1·2 to 2·6)	0·3 (−0·5 to 1·1); p=0·50
Number of pad change leaks per week														
Week 0	159	4·3 (6·7)	..	112	3·8 (4·4)	..	..	153	4·0 (6·0)	..	118	4·2 (5·7)	..	..
Week 24	149	1·8 (4·3)	−2·8 (−4·0 to −1·5)	107	2·3 (6·2)	−1·6 (−3·4 to 0·1)	−1·1 (−3·3 to 1·0); p=0·30	143	1·6 (5·2)	−2·0 (−3·3 to −0·7)	113	2·4 (5·0)	−2·3 (−4·1 to −0·6)	0·3 (−1·9 to 2·5); p=0·77
Number of leaks per day														
Week 0	159	1·7 (1·8)	..	112	1·4 (1·6)	..	..	153	1·5 (1·8)	..	118	1·6 (1·7)	..	..
Week 24	149	0·6 (1·1)	−1·2 (−1·5 to −0·8)	107	0·7 (1·3)	−1·0 (−1·5 to −0·5)	−0·1 (−0·7 to 0·4); p=0·61	143	0·5 (1·1)	−1·0 (−1·3 to −0·6)	113	0·8 (1·3)	−1·2 (−1·7 to −0·7)	0·2 (−0·4 to 0·8); p=0·50
MMHQ severity measures score														
Week 0	157	55·4 (24·3)	..	114	55·9 (24·0)	..	..	152	54·5 (23·8)	..	119	57·1 (24·6)	..	..
Week 24	136	36·5 (26·3)	−19·2 (−23·9 to −14·5)	101	41·2 (25·9)	−17·5 (−23·7 to −11·3)	−1·7 (−9·3 to 6·0); p=0·67	137	36·4 (25·8)	−17·1 (−21·9 to −12·2)	100	41·5 (26·4)	−19·6 (−25·8 to −13·4)	2·5 (−5·2 to 10·2); p=0·52

CRADI=Colorectal-Anal Distress Inventory. CRAIQ=Colorectal-Anal Impact Questionnaire. MMHQ=Modified Manchester Health Questionnaire.

Table 2: **Estimated outcomes at week 0 and 24 for loperamide versus oral placebo and biofeedback versus education (intention-to-treat)**

	Loperamide, n/N (%)	Placebo, n/N (%)	Adjusted odds ratio (95% CI)	Exercise plus biofeedback, n/N (%)	Education only, n/N (%)	Adjusted odds ratio (95% CI)
Patient Global Impression of Improvement (a little better, much better, or very much better)	127/146 (87%)	84/105 (80%)	1·2 (1·0–1·5); p=0·099	126/142 (89%)	85/109 (78%)	1·3 (1·0–1·6); p=0·046
50% reduction in leaks per day*	101/139 (73%)	73/102 (72%)	1·0 (0·8–1·2); p=0·83	113/135 (84%)	61/106 (58%)	1·4 (1·1–1·7); p=0·0009

*Endpoint analysis was done post hoc and not as part of the planned analysis.

Table 3: **Estimated outcomes at week 24 for loperamide versus oral placebo and biofeedback versus education (intention-to-treat)**

in the placebo plus biofeedback group due to not having the required colonoscopy screening documentation; one from the loperamide plus biofeedback group due to not having the required negative colon cancer screening documentation; one from the loperamide plus education group due to no documented colon cancer screening; and one from the loperamide plus education group due to previous pelvic radiation therapy). Data from these women were excluded from the analysis of the primary and secondary efficacy outcomes but were included in the safety analyses. The intention-to-treat analysis included data from 274 women at 12 weeks and 266 women at 24 weeks for whom outcome data were available.

There were no clinically important differences at baseline between groups or between participants with and without outcomes (table 1; appendix pp 3–8). There were also no clinically important differences at baseline between participants included in the intention-to-treat analysis and those included in the per-protocol analysis (data not shown). The median age of randomly assigned participants was 64·1 years (IQR 57·4–71·7). 234 (79%) of 296 participants were white, 46 (16%) were black, and 16 (5%) were another race or reported multiple races. 265 (90%) of 296 of participants were non-Hispanic, 26 (9%) were Hispanic, and five (1%) did not report an ethnicity. Despite an eligibility requirement of at least one episode of faecal incontinence per month over the preceding 3 months, participants reported a mean 1·6 (SD 1·8) leaks per day.

For the St Mark's score, no interaction between study drug and study therapy was observed (p=0·80). At 24 weeks, all groups showed some improvement in St Mark's score, although no significant marginal differences occurred between the medication and biofeedback groups in model-estimated difference from baseline to 24 weeks (model-estimated difference –1·5 [95% CI –3·4 to 0·4]; p=0·12 for loperamide *vs* placebo; –0·7 [–2·6 to 1·2]; p=0·47 for biofeedback *vs* education; table 2; appendix p 9). Neither were there differences between combination and individual treatments: combined loperamide plus biofeedback versus placebo plus biofeedback (model-estimated difference –1·9, 95% CI –4·1 to 0·3, p=0·092) or versus loperamide plus education (–1·1, –3·4 to 1·1, p=0·33; appendix p 12). The sensitivity analysis using multiply imputed data was consistent with these findings (appendix p 18). Similarly, in the per-protocol analysis there were no meaningful marginal differences at 24 weeks between the medication and biofeedback groups (appendix p 19). The combination of loperamide plus biofeedback showed some improvement in the St Mark's score at 24 weeks compared with placebo plus biofeedback (–3·8, –6·9 to –0·7, p=0·017) and compared with loperamide plus education (–3·5, –6·4 to –0·6, p=0·018; appendix p 22), but the differences were smaller than the minimally important difference.

Bowel diary outcomes improved in all groups. In the intention-to-treat analysis, participants assigned to combination therapy reported fewer pad changes per week due to stool leakage compared with those assigned to placebo plus biofeedback (model-estimated difference –2·6, –5·1 to –0·2, p=0·036; appendix p 13). In the per-protocol analysis, participants receiving the combination of treatments also had more faecal incontinence accident-free days per week (1·4, 0·2 to 2·7, p=0·028; appendix p 23) compared with those receiving placebo plus biofeedback.

Changes from baseline in CRADI, CRAIQ, and MMHQ severity were not different among any of the groups in the intention-to-treat analysis (table 2; appendix p 9). In marginal comparisons (comparisons between study therapies [pooled across study drugs] or between study drugs [pooled across study therapies]), more PGI-I scores were classified as a little better, much better, or very much better in the biofeedback group compared with education at 24 weeks (table 3). In the per-protocol analysis, participants receiving loperamide were more likely to report a little better, much better, or very much better improvement on the PGI-I at 24 weeks than those receiving placebo (77 [92%] of 84 *vs* 46 [79%] of 58, adjusted odds ratio 1·2, 95% CI 1·0–1·4, p=0·018; appendix p 20). In per-protocol analysis of combined versus single therapy, participants receiving combined treatment showed a greater improvement in CRADI scores at 24 weeks compared to the placebo plus biofeedback group (estimated difference –12·2, 95% CI –23·9 to –0·5, p=0·041; appendix p 22).

In the intention-to-treat analysis marginal comparisons, anal manometry measures including maximum anal canal resting pressure, volume of air at first sensation, or volume of air at strong urge at 24 weeks were not different between groups (table 4).

	Loperamide		Placebo		Model-estimated difference (95% CI)	Exercise plus biofeedback		Education only		Model-estimated difference (95% CI)
	N	Adjusted mean (SD) or mean (95% CI)	N	Adjusted mean (SD) or mean (95% CI)		N	Adjusted mean (SD) or mean (95% CI)	N	Adjusted mean (SD) or mean (95% CI)	
Maximum anal canal pressure (rest), mmHg										
Week 0	159	48·1 (17·3)	113	49·4 (20·5)	..	154	49·2 (19·2)	118	47·8 (17·8)	..
Week 24	145	46·7 (43·1 to 50·2)	104	47·2 (42·5 to 51·8)	−0·5 (−6·2 to 5·2); p=0·8659	140	47·8 (44·1 to 51·4)	109	46·1 (41·5 to 50·7)	1·7 (−4·1 to 7·4); p=0·5667
Maximum anal canal pressure (squeeze), mmHg										
Week 0	159	71·6 (32·1)	113	74·2 (34·9)	..	154	75·3 (34·9)	118	69·3 (30·7)	..
Week 24	143	75·1 (68·9 to 81·2)	104	73·7 (65·6 to 81·7)	1·4 (−8·4 to 11·2); p=0·7788	139	78·8 (72·5 to 85·1)	108	69·9 (61·9 to 77·9)	8·9 (−1·0 to 18·9); p=0·0780
Volume of air at first sensation, mL										
Week 0	159	26·9 (17·4)	112	25·8 (19·0)	..	153	25·8 (17·5)	118	27·3 (18·8)	..
Week 24	143	20·9 (17·9 to 23·8)	105	24·0 (20·1 to 27·8)	−3·1 (−7·8 to 1·6); p=0·1970	139	22·3 (19·3 to 25·4)	109	22·5 (18·7 to 26·3)	−0·2 (−5·0 to 4·5); p=0·9233
Volume of air at strong urge, mL										
Week 0	157	77·7 (35·7)	110	80·9 (36·8)	..	151	79·8 (36·7)	116	78·0 (35·4)	..
Week 24	142	76·7 (70·8 to 82·5)	104	75·7 (68·1 to 83·4)	0·9 (−8·4 to 10·3); p=0·8450	137	77·2 (71·2 to 83·2)	109	75·2 (67·6 to 82·7)	2·0 (−7·5 to 11·5); p=0·6793

Table 4: **Estimated outcomes for loperamide versus oral placebo and biofeedback versus education (intention-to-treat)**

Participants assigned to combination therapy had higher maximum anal canal squeeze pressures (in mm Hg) than those assigned to loperamide plus education (15·9, 95% CI 4·2–27·7, p=0·00082; appendix p 14). In the per-protocol analysis marginal comparisons, there were higher maximum anal canal squeeze pressures among those receiving biofeedback versus education (20·3, 6·9–33·7, p=0·0033; appendix p 21). Participants receiving combination therapy had higher maximum anal canal squeeze pressures than those receiving loperamide plus education (29·6, 13·3–45·9, p=0·0005; appendix p 24) at 24 weeks.

The percentage of participants with any adverse event was highest in the loperamide and biofeedback group (72 [84%] of 86) compared with placebo and biofeedback (62 [74%] of 84), loperamide plus education (62 [70%] of 88), or placebo plus education (26 [62%] of 42; p=0·042; table 5) The proportion of participants reporting a gastrointestinal event was not different among groups, and ranged from 19 (45%) of 42 in the placebo-education only group to 54 (63%) of 86 in the loperamide plus biofeedback group (appendix p 28). Constipation was the most common adverse event and was reported more in the groups assigned to loperamide (33 [38%] of 88 loperamide plus education and 44 [51%] of 86 for loperamide plus biofeedback) than in the two groups assigned to placebo (five [12%] of 42 for placebo plus education and 19 [23%] of 84 for placebo plus biofeedback; p<0·0001 for comaprison across the four groups; appendix p 28). Participants in the per-protocol population were less likely to report constipation compared with participants who did not follow the protocol (52 [27%] of 193 *vs* 49 [46%] of 107, p=0·0014). The percentage of participants with any grade 3 or higher adverse events did not differ between the treatment groups (table 5). Constipation was the most common grade 3 or higher adverse event and was reported by four participants (two in each of the loperamide groups). The percentage of participants with any serious adverse events did not differ between the treatment groups (table 5). Only one serious adverse event was considered possibly related to treatment (small bowel obstruction in the placebo plus biofeedback group).

Discussion

The intention-to-treat analysis did not show a difference in the change in St Mark's score for either loperamide or manometry-directed biofeedback alone or in combination for the treatment of faecal incontinence after 24 weeks of treatment. Participants had greater reduction in faecal incontinence severity in the control group (placebo plus education) than anticipated, which might be due to a higher than anticipated effect of a simple educational pamphlet in women with faecal incontinence. This finding highlights the importance of a control group in high-quality randomised trials and the potential efficacy of standardised education alone in the treatment of faecal incontinence.

There were some differences between the groups in important exploratory secondary outcomes. Participants randomly assigned to combination therapy had fewer pad changes per week due to stool leakage, and participants assigned to biofeedback plus education at 24 weeks each reported significantly higher proportion of PGI-I scores of a little, much, or very much better compared with education only. Although important secondary clinical outcomes showed some improvement, they should be interpreted with caution given the chance of making

	Placebo–exercise plus biofeedback (N=84)	Placebo–education only (N=42)	Loperamide–exercise plus biofeedback (N=86)	Loperamide–education only (N=88)	p value
Any adverse event					
Participants with any adverse event, n (%)	62 (74%)	26 (62%)	72 (84%)	62 (70%)	0·042
Total number of adverse events per person					
Mean (SD)	2·1 (0·2)	2·0 (0·4)	2·7 (0·3)	2·7 (0·3)	0·29
Median (range)	1 (0–9)	2 (0–10)	2 (0–20)	2 (0–17)	..
Adverse events per month					
Mean (SD)	0·38 (0·04)	0·38 (0·07)	0·51 (0·06)	0·48 (0·06)	0·31
Median (range)	0·2 (0·0–1·6)	0·3 (0·0–1·7)	0·4 (0·0–3·4)	0·3 (0·0–3·1)	..
Participants with an adverse event, n (%)*	..	..	..	..	0·20
Mild	22 (26%)	7 (17%)	21 (24%)	14 (16%)	..
Moderate	34 (40%)	15 (36%)	43 (50%)	35 (40%)	..
Severe	5 (6%)	3 (7%)	8 (9%)	11 (13%)	..
Life threatening	0 (0%)	1 (2%)	0 (0%)	2 (2%)	..
Fatal	1 (1%)	0 (0%)	0 (0%)	0 (0%)	..
Grade 3 or higher adverse events					
Participants with any adverse event, n (%)	6 (7%)	4 (10%)	8 (9%)	13 (15%)	0·43
Total number of adverse events per person					
Mean (SD)	0·1 (0·0)	0·1 (0·1)	0·1 (0·0)	0·2 (0·1)	0·33
Median (range)	0 (0–2)	0 (0–3)	0 (0–2)	0 (0–5)	..
Serious adverse events					
Participants with any serious adverse event, n (%)	5 (6%)	3 (7%)	6 (7%)	10 (11%)	0·62
Total number of serious adverse events per person					
Mean (SD)	0·1 (0·0)	0·1 (0·1)	0·1 (0·0)	0·1 (0·0)	0·50
Median (range)	0 (0–1)	0 (0–3)	0 (0–1)	0 (0–2)	..

p values were obtained using analysis of variance (ANOVA) techniques for continuous measures, Mantel-Haenszel mean score tests using modified ridit scores for ordinal measures, and Fisher exact tests for categorical measures. *Participants counted only once for highest severity reported for adverse events.

Table 5: **Adverse events**

erroneous inferences during multiple comparisons as well as regression to the mean or selective drop out.

Faecal incontinence can be defined in several ways. The definition for this trial was most consistent with the International Continence Society's definition of involuntary loss of solid or liquid stool. The Rome III definition of faecal incontinence was not formally used for eligibility for this trial, because it did not describe the type of stool (liquid or solid) and was considered too cumbersome to implement in a primary-care setting.

The choice of using the St Mark's score was thoroughly investigated by the research team. At the time of study development, the St Mark's score was one of few patient-reported outcome measures that had sufficient evidence of validity, reliability, and responsiveness to change in faecal incontinence symptoms. However, we did not report results of individual questionnaire items within the St Mark's score, because these items have differing levels of validity and reliability and were not prespecified.

This study was one of the largest randomised controlled trials of loperamide in women that included multisite investigation of manometry-guided biofeedback for the treatment of faecal incontinence. These two treatments are thought to reduce faecal incontinence through two distinct mechanisms: loperamide modifies stool consistency, transit time, and rectal urgency indirectly and biofeedback is a teaching tool to increase anal sphincter muscle strength and rectal sensation. Because these treatment mechanisms are distinct, synergy is a possibility, which is why single and combined therapies were compared.

Loperamide reduces faecal incontinence either alone[8,9] or combined with increased dietary fibre intake[36] for patients with diarrhoea-related faecal incontinence. A randomised controlled trial comparing biofeedback to loperamide and to the two treatments combined showed no difference between loperamide and biofeedback, but the combined treatment improved continence relative to baseline.[37] No placebo or sham treatment was used in this trial, so the possibility of a placebo effect cannot be excluded. This study compared loperamide to an oral placebo and did not show a significant benefit.

Previous biofeedback interventions have been criticised as not being rigorously applied. The biofeedback training protocol used in this study was adapted from a previous single-site randomised controlled trial that showed treatment benefit and was rigorously used.[36] The protocol

divided the training into more easily discriminated components (strength training, increased perception for patients with loss of rectal sensation, and increased tolerance for rectal distention in patients with hypersensitivity for rectal filling).[14] The training software was also modified by including instructions to the interventionist on how to perform the procedure. A centralised system for training the interventionists and testing their adherence to the protocol was also developed.[14] However, the change in St Mark's score from baseline to 24 weeks was similar in the biofeedback groups compared with the other groups. Thus, despite the efforts invested in improving the biofeedback training protocol, these data question the effectiveness of a more invasive and expensive biofeedback intervention, which requires expertise, for the treatment of faecal incontinence.

Despite the large sample size and rigorous design, our findings are limited in scope. To follow the intention-to-treat principle as closely as possible, all participants were kept in their originally assigned groups for analysis. However, outcome data could not be obtained on some participants (figure), which precluded a strict intention-to-treat analysis. Almost all of the statistically significant results were found in the per-protocol analyses. However, these results should be interpreted with considerable caution. First, per-protocol analyses omit non-compliant patients and dropouts, whose outcomes might be quite different from those of compliant participants. Per-protocol analyses do not inherit the key benefits of randomisation to prevent confounding and in this study adherence was reduced at 24 weeks (eg, 33 [39%] of 85 in the loperamide plus biofeedback group). Second, most of the significant p values were for secondary outcomes, and the manometry findings should interpreted with caution, because interventionists who did the manometry on all participants were only masked to the medication intervention allocation and not to the biofeedback intervention allocation. Third, no adjustment was made for multiple comparisons. The study had reduced power to detect a difference as large as the minimally important difference in the combined treatment group versus loperamide or biofeedback alone; however, the observed differences were considerably smaller than the minimally important difference. This study found a larger than expected response in the placebo plus education group that is not explained by the effects of education or placebo alone. Preplanned secondary analyses of risk factors for treatment failure will be done to try to understand why some participants did not respond to treatment. Fourth, in contrast to most previous studies that enrolled men and women, this trial exclusively enrolled women, and the results should be extrapolated to treatment of faecal incontinence in men with caution. Finally, we elected to allow participants to follow a strict algorithm of dose escalation and reduction using loperamide or placebo, because dose escalation and reduction is part of routine care when prescribing loperamide and since the specific dose for patients with faecal incontinence and normal stool consistency was unknown. However, the details regarding these dose adjustments are not presented here and might be useful for future analyses.

In conclusion, we were unable to find evidence against the null hypotheses that loperamide is equivalent to placebo, that anal exercises with biofeedback is equivalent to an educational pamphlet, and that loperamide and biofeedback together are equivalent to oral placebo and biofeedback or loperamide plus an educational pamphlet in women with normal stool consistency and faecal incontinence that was bothersome enough to seek treatment. Some benefits were observed with combined treatments compared with individual treatments. Although the proportion of participants reporting a gastrointestinal event was not different between groups, constipation was the most common adverse event. Additional studies that account for a substantial oral placebo or education response and low treatment adherence will be needed to adequately assess these commonly used primary treatments for faecal incontinence. Because these are common first-line treatments for faecal incontinence, clinicians could consider combining loperamide, anal manometry-assisted biofeedback, and a standard educational pamphlet, but this is likely to result in only negligible improvement over individual therapies and patients should be counselled regarding possible constipation.

Contributors

All authors contributed to the literature search, figures, study design, data collection, data analysis, data interpretation and writing. BC and MGG did the statistical analysis and the senior statistician (MGG) vouches for the accuracy of the reported data and for the fidelity of the study.

Declaration of interests

Equipment was purchased at or below cost from Medspira by RTI on behalf of the Pelvic Floor Disorders Network in return for the Network providing consultation on mcompass biofeedback software modifications. Medspira had no input into the design, implementation, data collection or analysis of this trial. JEJ reports grant support from the National Institute of Child Health and Human Development (NICHD) Pelvic Floor Disorders Network. MDB reports grants from NICHD, during the conduct of the study, and personal fees from Boston Scientific, Elsevier, and UpToDate, outside the submitted work. DKN reports grants from National Institutes of Health, during the conduct of the study. RGR reports grants from NICHD, during the conduct of the study, and personal fees from Uptodate, outside the submitted work. RGR has also received stipend and travel from the American Board of Obstetrics and Gynecology for work on the board, stipend and travel from IUGA for work on the International Urogynecology Journal, and honorarium and travel for attending committees and lectures from American College of Obstetrics and Gynecology. KD reports research support from Pevalon. AGV reports other from NinoMed, outside the submitted work. HMZ reports grants from NICHD, during the conduct of the study. SFM was an employee of the National Institutes of Health. MGG reports grants from NICHD and other from Medspira, during the conduct of the study. All other authors declare no competing interests.

Data sharing

Deidentified participant data and a data dictionary will be made available in the the NICHD's Data and Specimen Hub (DASH), and criteria for sharing data will be per DASH policies. DASH requires institutional

For the **Data and Specimen Hub** see https://dash.nichd.nih.gov/

certification, protocol, case report forms, data dictionary, format codebook, and de-identified participant data. When available, statistical analysis plans and lists of publications are also provided. We expect the data to be available within 6 months after publication.

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