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Review

A systematic review and network meta-analysis comparing treatments for faecal incontinence

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ABSTRACT

Background: Although numerous treatments exist for fecal incontinence (FI), no consensus exists on the best treatment strategy. The aim was to review the literature and to compare the clinical outcomes and effectiveness of treatments available for FI.

Materials and method: A systematic literature review was performed, from inception to May 2018, of the following databases: MEDLINE, EMBASE, Science Citation Index Expanded, Cochrane Library. The search terms used were "faecal incontinence" and "treatment". Only randomized controlled trials (RCTs) comparing treatments for FI were considered. A Bayesian network meta-analysis was performed using the Markov chain Monte Carlo method.

Result: Forty-seven RCTs were included comparing 37 treatments and reporting on 3748 participants. No treatment ranked best or worst with high probability for any outcome of interest. No significant difference was identified between treatments for frequency of FI per week, or in changing the resting pressure, maximum resting pressure, squeeze pressure, and maximum squeeze pressure. Radiofrequency resulted in more adverse events compared to placebo. Sacral nerve stimulation (SNS) and zinc-aluminium improved the fecal incontinence quality of life questionnaire (FIQL) lifestyle, coping, and embarrassment domains compared to placebo. Transcutaneous posterior tibial nerve stimulation (TPTNS) improved the FIQL embarrassment domain compared to placebo. Autologous myoblasts and zinc-aluminium improved the FIQL depression domain compared to placebo. SNS, artificial bowel sphincter (ABS), and zinc-aluminium significantly improved incontinence scores compared to placebo. Injection of non-animal stabilized hyaluronic acid/dextranomer (NASHA/Dx) resulted in more patients with $\geq 50\%$ reduction in FI episodes compared to placebo.

Conclusion: SNS, ABS, TPTNS, NASHA/Dx, zinc-aluminium, and autologous myoblasts resulted in isolated improvements in specific outcomes of interest. No difference was identified in incontinence episodes, no treatment ranked best persistently or persistently improved outcomes, and many included treatments did not significantly benefit patients compared to placebo. Large multicentre RCTs with long-term follow-up and standardized inclusion criteria and outcome measures are needed.

1. Introduction

Faecal incontinence (FI) can range from an involuntary passage of flatus to complete evacuation of liquid or solid faecal matter, and depending on the severity of the disease, it can be psychologically and socially debilitating. To date, many randomized controlled trials (RCTs) have been published comparing the treatments available for FI without concrete results and without a clear treatment strategy [1–47]. An important disadvantage of these RCTs, and of standard pairwise meta-analyses, published on this subject [48,49], is that they can only compare two treatments directly, rather than all available treatments at once. A network meta-analysis allows simultaneous comparison of all treatments available for FI [50,51]. Furthermore, a network meta-analysis may yield more reliable and definitive results, and allows us to visualize and interpret a wider picture of the available evidence, and to calculate treatment rankings with probabilities [50,51]. The aim of the present study was to perform a systematic review of the literature to identify treatments available for FI, collect all published data from

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RCTs, and perform a network meta-analysis to compare the clinical outcomes and effectiveness of treatments available for FI.

2. Materials and methods

2.1. Search strategy

This systematic review and meta-analysis was based on a written protocol and was reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [52] and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [53]. A comprehensive literature search was performed of the following databases: MEDLINE, EMBASE, Science Citation Index Expanded, and Cochrane Central Register of Controlled Trials (CENTRAL). Detailed search strategy is provided in the Supplementary Table 1. No restrictions were made based on language, publication year, or publication status. The latest date for this search was May 17th, 2018.

2.2. Inclusion and exclusion criteria

Only RCTs were considered for this network meta-analysis. In order to be included in the analysis, RCTs had to report on at least one of the outcomes of interest and compare two or more treatments, or a combination of different treatments for FI in adults. Studies were excluded from the analysis if: (a) the outcomes of interest were not clearly reported, and it was impossible to extrapolate or calculate the necessary data from the published results; (b) the studies were published only as conference abstracts; (c) the studies included patients with other disorders (e.g. rectal prolapse, anal fissures) who did not suffer specifically with faecal incontinence; (d) the studies reported on patients with ileoanal and coloanal anastomosis; (e) the studies reported on outcomes only on the day of the treatment without a follow-up of more than one day.

2.3. Data extraction

Two review authors (CS and NL) independently determined the eligibility of the retrieved studies and extracted the review data. The risk of bias of the included studies was assessed based on the following bias risk domains: allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and vested interest bias [54]. For each of these risk domains of bias, the studies were categorized as low risk, uncertain risk and high risk of bias.

2.4. Outcomes of interest

1. *Adverse events.* Adverse events were defined as any deviation from the normal postoperative course.
2. *Quality of Life outcomes.* The faecal incontinence quality of life questionnaire (FIQL) was used [55].
3. *Functional outcomes.* The following functional outcomes were used for comparison: frequency of FI episodes per week, 50% or more reduction in the number of FI episodes, and incontinence score. For the purpose of this network meta-analysis, the Vaizey or St Mark's score (out of 24) [56] was standardized to match the Wexner or Cleveland clinic incontinence (CCI) score (out of 20) [57].
4. *Anal manometry.* The following anal manometry outcomes were used for comparison: resting pressure, maximum resting pressure, squeeze pressure, and maximum squeeze pressure.

2.5. Statistical analysis

For each outcome of interest, Stata/IC 11 (StataCorp LP, College Station, Texas, USA) was used to draw a network plot of all the treatments assessed for that specific outcome. Any treatments not connected to the other treatments through the network plot were excluded from the analysis of that outcome. A Bayesian network meta-analysis was conducted using the Markov chain Monte Carlo method in WinBUGS 1.4 (MRC Biostatistics Unit, Cambridge, and Imperial College School of Medicine, London, UK). For binary data, a binomial model was used for the analysis, and the odds ratio (OR) was calculated. For continuous outcomes, the mean difference (MD) was calculated. The treatment contrast for any two treatments was modelled as a function of comparisons between each individual treatment and an arbitrarily selected reference group. The probability of ranking of a treatment (i.e. that a treatment ranks as the best treatment, second best treatment, etc.) for each outcome of interest was calculated.

The residual deviance and deviance information criterion (DIC) were used for assessing between-study heterogeneity [58]. Three different models were run for each outcome: fixed-effect model, random-effects model and random-effects inconsistency model. The choice of model was based on the model fit and the DIC provides a measure of model fit that penalizes model complexity; therefore, a lower DIC indicated a better model fit [58]. Evidence of inconsistency between direct and indirect comparisons was assessed by examining the geometry of the network diagrams [59] and by comparing the deviance and DIC statistics of the consistency and inconsistency models to assess which model resulted in a better model fit [59].

3. Results

3.1. Eligible studies

A total of 3009 references were identified through systematic electronic searches of Science Citation Index Expanded (n = 227), EMBASE (n = 468), MEDLINE (n = 1851) and CENTRAL (n = 463). Further four studies were identified from the references of the above studies. The duplicates between databases were 590 and were excluded. Further 2311 clearly irrelevant references were excluded through screening titles and reading abstracts. The remaining 112 studies were investigated in full text detail and further 65 studies were excluded. Fig. 1 shows the study flow diagram. Forty-seven RCTs comparing treatments for FI fulfilled the inclusion criteria of this network meta-analysis [1–47]. The characteristics of the included studies, including the treatments compared and patient demographics for individual studies, are summarized in Table 1. The risk of bias in the included studies is summarized in Fig. 2 and the risk of bias for each included study is shown in Supplementary Fig. 1. The included RCTs were categorized as low risk of bias for most of the bias risk domains assessed, except for performance bias and detection bias [54].

3.2. Overall analysis

There were 3748 patients for analysis having undergone 37 different treatments for FI. The reported mean age of the patients ranged from 32 to 84 years, and there were 530 males and 3218 females. An example of a network plot for incontinence score is shown in Fig. 3; similar network plots were constructed for all outcomes of interest. The treatments included in the network meta-analysis for each outcome of interest are shown in Table 2. For all outcomes of interest, the fixed-effect model was preferred based on the DIC statistics, and there was no evidence of inconsistency between trials in the networks. All statistically significant results of the pairwise comparisons of the different treatments for all outcomes are shown in Table 3. The treatments with the highest probability of ranking best or worst treatment for the outcomes of interest are summarized in Table 4. There was substantial uncertainty regarding the best or worst treatment for all outcomes as no treatment highlighted a probability of greater than 90% [60].

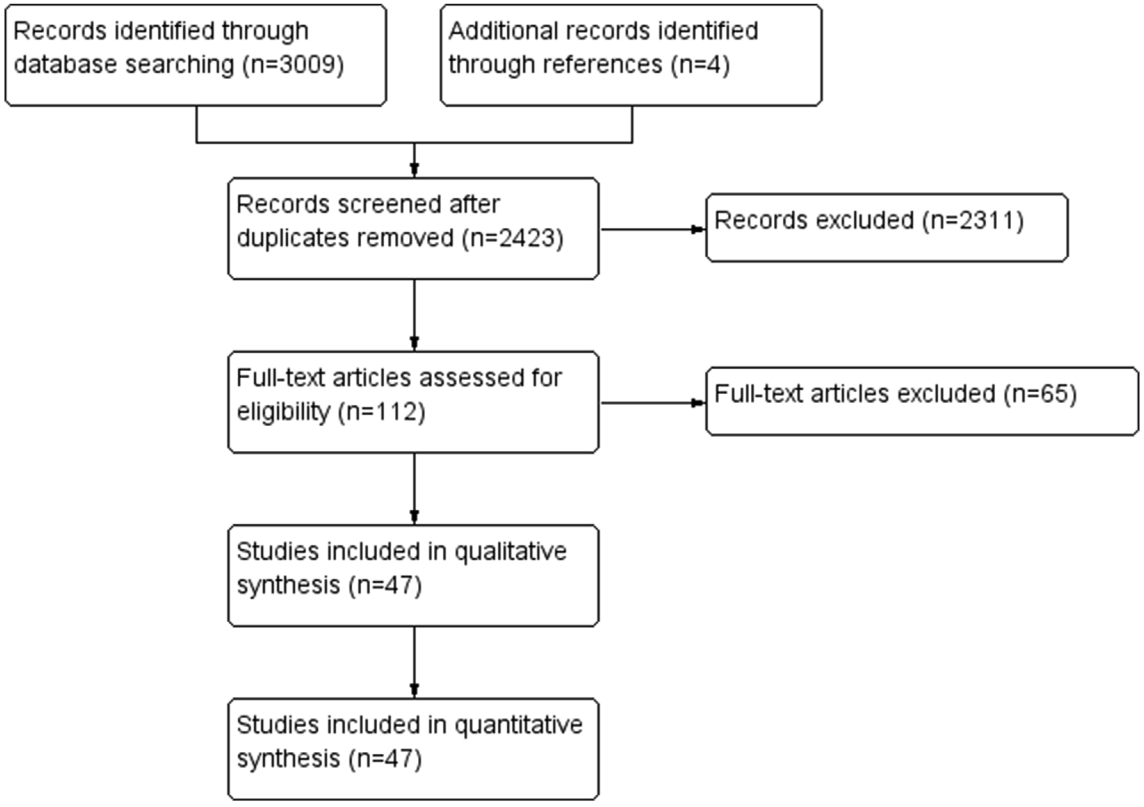

Fig. 1. Study flow diagram.

3.3. Adverse events

Forty-three trials provided data on 3277 participants and 31 treatments, for the network meta-analysis on adverse events. Pairwise comparisons of the treatments demonstrated significantly more adverse events with transanal delivery of radiofrequency energy compared to placebo. No other significant difference in adverse events was identified between treatments.

3.4. Quality of life

Sixteen trials (1397 participants; 14 treatments) provided data for the network meta-analysis on quality of life using the FIQL questionnaire. Separate network meta-analyses were performed for the four domains of the FIQL: lifestyle, coping, depression, and embarrassment.

Pairwise comparison of treatments with regards to FIQL-lifestyle scores found that sacral nerve stimulation (SNS) resulted in significant improvement in the lifestyle domain compared to placebo. Also, zinc-aluminium ointment resulted in significant improvement in the lifestyle domain compared to placebo, clonidine, biofeedback-pelvic floor muscle training (BF-PFMT), BF-PFMT plus medical management (use of antidiarrheal medications and laxatives), BF-PFMT plus electrical stimulation, elastomer implants, injection of non-animal stabilized hyaluronic acid/dextranomer (NASHA/Dx), transcutaneous posterior tibial nerve stimulation (TPTNS), percutaneous posterior tibial nerve stimulation (PPTNS), and Permacol injection. There was no significant difference in the other comparisons for this domain.

Similarly, pairwise comparison for the FIQL-coping domain showed SNS to have significant improvement compared to placebo, and zinc-aluminium ointment to have significant improvement compared to placebo, TPTNS, PPTNS, and Permacol. For the FIQL-depression domain, injection of autologous myoblasts resulted in significant improvement compared to placebo, and zinc-aluminium ointment resulted in significant improvement compared to placebo, BF-PFMT, BF-PFMT plus electrical stimulation, NASHA/Dx, TPTNS, PPTNS, and Permacol. In addition, zinc-aluminium ointment demonstrated significant improvement during pairwise comparisons for the FIQL-embarrassment domain compared to placebo and autologous myoblasts. Pairwise comparison for the FIQL-embarrassment domain also found SNS to result in significantly better score compared to placebo, PPTNS, and autologous myoblasts injection. TPTNS was found to have significantly improved FIQL-embarrassment domain score compared to placebo.

3.5. Incontinence score

Thirty-one trials reporting on 2381 patients and 25 treatments were included in the network meta-analysis for comparing changes in incontinence scores. Artificial bowel sphincters (ABS) ranked best with 81.7% probability for this outcome.

Pairwise comparisons demonstrated that ABS significantly improved incontinence score compared to placebo, advice alone, topical 1R-2S-methoxamine hydrochloride (NRL001), medical management, BF-PFMT plus medical management, transanal irrigation, elastomer implants, NASHA/Dx, PPTNS, Permacol, and Bulkamid. Moreover, SNS was found to improve incontinence score significantly compared to placebo, NRL001, medical management (antidiarrheal medications and laxatives), BF-PFMT plus medical management, transanal irrigation, Permacol, and Bulkamid injection. Use of zinc-aluminium significantly improved incontinence score compared to placebo, NRL001, medical management, BF-PFMT plus medical management, transanal irrigation, Permacol, and Bulkamid injection.

Medical management alone resulted in significantly worse incontinence score compared to placebo, NRL001, phenylephrine, oestrogen, PFMT with digital rectal feedback (DRF), BF-PFMT, electrical stimulation alone, BF-PFMT plus electrical stimulation, NASHA/Dx, PPTNS, TPTNS, and autologous myoblasts injection. In addition, BF-PFMT plus medical management was noted to have significantly worse incontinence score compared to placebo, advice alone, NRL001,

Table 1
Summary of study characteristics. Footnotes: N = Total Number of Participants in the Study, T = Treatment, C = Control, CMC = Carboxymethylcellulose, GA = Gum Arabic, BF = Biofeedback, RBT = Rectal Balloon Training, PFMT = Pelvic Floor Muscle Training, DRF- Digital Rectal Feedback, TPTNS = Transcutaneous Posterior Tibial Nerve Stimulation, TPFR = Total Pelvic Floor Repair, NRL001 = 1R,2S-methoxamine hydrochloride, SNS = Sacral Nerve Stimulation, PPTNS = Percutaneous Posterior Tibial Nerve Stimulation, NASHA/Dx = Injection of Non-Animal Stabilized Hyaluronic Acid/Dextranomer, FI = Faecal Incontinence, EMG = Electromyography, freq = frequency, min = Minutes, NR = Not Reported.

Study	Mean age	Aetiology	Treatments	N	Follow-up	Treatment duration
Bharucha et al. 2014[3]	58	Mixed	T: Clonidine	T-22	4 weeks	4 weeks
			C: Placebo medication	C-22		
Bliss et al. 2001[4]	61	NR	T1: Psyllium	T1-13	31 days	31 days
			T2: GA	T2-13		
			C: Placebo	C-13		
Bliss et al. 2014[5]	58	Mixed	T1: CMC	T1-53	38 days	38 days
			T2: GA	T2-50		
			T3: Psyllium	T3-49		
			C: Placebo diet	C-46		
Bols et al. 2011[6]	59	Mixed	T: BF-RBT and PFMT	T-40	4.5 months	9 weeks
			C: PFMT (With DRF)	C-40		
Booth et al. 2013[7]	84.2	Mixed	T: TPTNS	T-15	8 months	8 months
			C: Sham intervention	C-16		
Bouguen et al. 2014[8]	65	Mixed	T: TPTNS	T-10	5 months	5 months
			C: Sham intervention	C-9		
Boyer et al., 2018[9]	52	Structural	T: Autologous myoblasts injection	T-12	12 months	One injection
			C: Placebo injection	C-12		
Carapeti et al. 2000[10]	58	Mixed	T: Phenylephrine	T-18	4 weeks	4 weeks
			C: Placebo medication	C-18		
Christensen et al. 2006[11]	49	Neurogenic	T: Transanal irrigation	T-42	10 weeks	10 weeks
			C: Conservative bowel management	C-45		
Cohen-Zubary et al. 2015[12]	67.5	Structural	T: Home electrical stimulation	T-22	6 weeks	6 weeks
			C: BF	C-20		
Damon et al. 2014[13]	61	Structural	T: BF-PFMT + Standard care	T-77	4 months	NR
			C: Standard care-medical management	C-80		
Deen et al., 1993[15]	51	Neurogenic	T1: TPFR	T1-12	6 months, 2 years	Surgery
			T2: Anterior levatorplasty	T2-12		
			T3: Postanal repair	T3-12		
			C: Patients undergoing hernia repair or cholecystectomy served as controls			
Deen et al. 1995[14]	56	Neurogenic	T: Internal Anal Sphincter Plication and TPFR	T-15	4.5 months, 5,5 months	Surgery
			C: TPFR alone	C-18		
Dehli et al. 2013[16]	57.5	Mixed	T: NASHA/Dx injection	T-64	6 months	6 months
			C: BF-PFMT	C-62		
Fynes et al. 1999[17]	32	Structural	T: BF-PFMT (anal EMG) + electrical stimulation 25 min/week	T-20	3 months	3 months
			C: BF-PFMT (vaginal EMG) 30 min/week	C-20		
George et al. 2013[18]	57	Structural	T1: PPTNS	T1-11	6 weeks	6 weeks
			T2: TPTNS	T2-11		
			C: Sham transcutaneous	C-8		
Graf et al. 2011[19]	61	Mixed	T: NASHA/Dx injection	T-136	3 months, 6 months, 1 year	Injection (1d)
			C: sham injections	C-70		
Healy et al. 2006[20]	54	Mixed	T: Endo-anal pudendal electrical stimulation	T-25	3 months	3 months
			C: BF/electrical stimulation treatment	C-23		
Heymen et al. 2009[21]	60	Structural	T: BF-PFMT with intra-rectal balloon distension	T-83	3 months, 6 months, 1 year	3 months
			C: PFMT	C-85		
Kahlke et al. 2015[22]	55.5	Mixed	T: SNS: ON C: SNS: OFF	T-8	4.5 months	6 weeks
				C-8		
Knowles et al. 2015[23]	58	Structural	T: PPTNS	T-115	12 weeks	12 weeks
			C: Sham stimulation	C-112		
Leroi et al. 2005[24]	57	Mixed	T: SNS: ON C: SNS: OFF	T-27	1 month, 2 months	1 month (each crossover)
				C-27		
Leroi et al. 2012[25]	60	Structural	T: TPTNS	T-73	3 months	3 months
			C: Sham stimulation	C-71		
Maeda et al. 2008[26]	68	Structural	T: Elastomer	T-5	6 months	One injection
			C: Permacol	C-5		
Mahony et al. 2004[27]	34	Structural	T: BF-PFMT(EMG) plus electrical stimulation	T-30	12 weeks	12 weeks (6 + 6)
			C: BF-PFMT(EMG)	C-30		
Markland et al.2015[28]	61	Structural	T: Loperamide (plus psyllium powder placebo)	T-43	15 weeks	4 × 4 weeks
			C: Psyllium powder (plus loperamide placebo)	C-37		
Naimy et al. 2007[29]	36	Structural	T: BF (EMG)−PFMT with electrical anal stimulation	T-24	8 weeks	8 weeks
			C: BF-PFMT(EMG)	C-25		
Norton et al. 2003[30]	56	Structural	T1: Hospital and home- based BF-PFMT plus advice	T1-29	1 year	3–6 months
			T2: Hospital-based BF-PFMT plus advice	T2-32		
			T3: PFMT with DRF plus advice	T3-44		
			C: Standard care (advice)[d]	C-35		
Norton et al. 2006[31]	55	Mixed	T: Anal stimulation at 35 Hz and 43 Hz	T-47	8 weeks	8 weeks
			C: Sham stimulation at 1 Hz	C-43		

(*continued on next page*)

Table 1 (*continued*)

Study	Mean age	Aetiology	Treatments	N	Follow-up	Treatment duration
O' Brien et al.2004[32]	63	Mixed	T: Artificial bowel sphincter (Acticon Neosphincter®) C: Supportive care, physiotherapy of the pelvic floor, anal sphincter muscle rehab, BF, electrical stimulation	T-7 C-7	3 months, 6 months	Neosphincter insertion surgery
Osterberg et al. 2004[33]	66	Neurogenic	T: Anterior levatorplasty (postanal repair for men) C: Anal plug electrical stimulation of the pelvic floor	T-35 C-35	3 months, 1 year, 2 years	1 day-5weeks
Pinedo et al. 2009[34]	69	NR	T: Topical oestrogens C: Placebo	T-18 C-18	6 weeks	3/day for 6 weeks
Pinedo et al. 2012[35]	61	NR	T: Zinc–aluminum ointment C: Placebo	T-25 C-25	1 month	1 month
Read et al. 1982[36]	45	Mixed	T: Loperamide C: Placebo	T-26 C-26	1 week, 2 weeks	1 week each
Rydningen et al. 2017[37]	61	Structural	T: SNS C: submucosal injection of collagen (Permacol)	T-30 C-26	6 months	6 months
Sarveazad et al. 2017[38]	37	Mixed	T: Human adipose-derived stromal/stem cells C: Placebo	T-9 C-9	8 weeks	injection
Schwandner et al. 2010[39]	63	Mixed	T: BF-PFMT (EMG) plus electrical stimulation (triple target) C: EMG- BF alone	T-79 C-79	9 months	9 months
Siproudhis et al. 2007[41]	64.5	Mixed	T: Polydimethylsiloxane elastomer C: Physiological saline	T-22 C-22	3 months	1/month
Siproudhis et al. 2016[40]	62	Mixed	T1: 5 mg NRL001 T2: 7.5 mg NRL001 T3: 10 mg NRL001 C: Placebo	T1-114 T2-115 T3-122 C-112	8 weeks	Once daily over 8 weeks
Sjodahl et al. 2015[42]	60	Structural	T: Laxative and Loperamide C: BF	T-33 C-31	6–8 months	4–6 months of BF, 2 months of medical treatment
Solomon et al. 2003[43]	62	Mixed	T1: BF-PFMT with transanal ultrasound T2: BF-PFMT with anal manometry, C: PFMT with digital guidance	T1-40 T2-39 C-41	4.5 months	9 weeks
Sun et al. 1997[44]	56	Mixed	T: Loperamide C: Placebo	T-11 C-11	2 weeks, 4 weeks	1 week each
Thin et al. 2015[45]	59	Mixed	T1: PPTNS C: SNS	T-16 C-15	3 months, 6 months	5 months
Tjandra et al. 2008[46]	63	Mixed	T: SNS C: PFMT, bulking agent (Imodium) and dietary manipulation	T-53 C-60	3 months, 6 months, 1 year	1 day to 1 year
Van der Wilt et al. 2017[47]	65	Mixed	T: PPTNS C: sham electrical stimulation	T-29 C-30	12 months	9 weeks
Visscher et al. 2017[48]	62	Mixed	T: Radiofrequency energy C: Sham procedure	T-20 C-20	6 months	One procedure
Yoshioka et al. 1999[49]	60	Structural	T: TPFR C: Gluteus Maximus Transposition	T-12 C-12	18 months	Surgery

phenylephrine, oestrogen, PFMT-DRF, BF-PFMT, BF (RBT) plus PFMT, electrical stimulation alone, BF-PFMT plus electrical stimulation, elastomer, NASHA/Dx, PPTNS, TPTNS, autologous myoblasts, and Bulkamid injection. Permacol resulted in significantly worse incontinence score compared to topical oestrogen and autologous myoblasts injection.

3.6. Frequency of faecal incontinence

Eleven trials provided data on 1178 participants and 10 treatments, for the network meta-analysis on the frequency of episodes of FI per week. No significant differences were observed between treatments during pairwise comparisons regarding the frequency of FI episodes per week. Only five trials (566 participants; 5 treatments) provided data for the network meta-analysis on the decrease in the frequency of FI episodes per week by 50% or more. Pairwise comparisons demonstrated

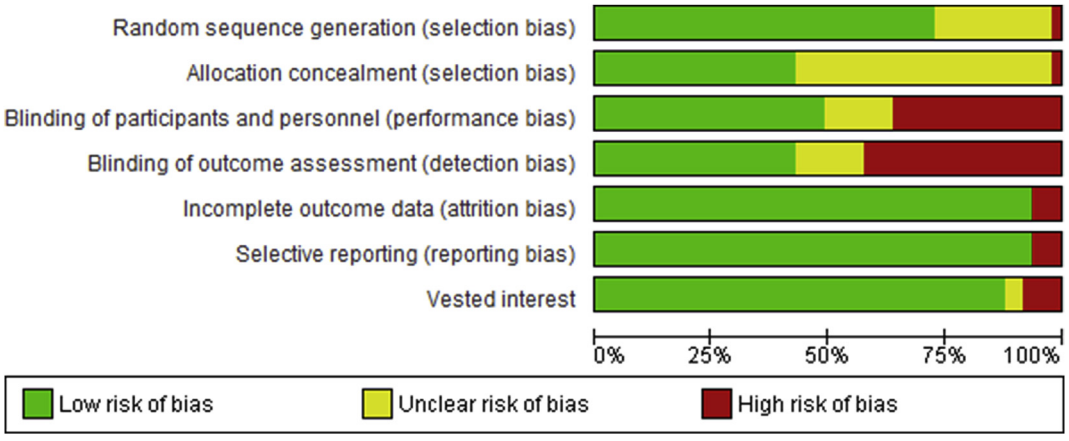

Fig. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

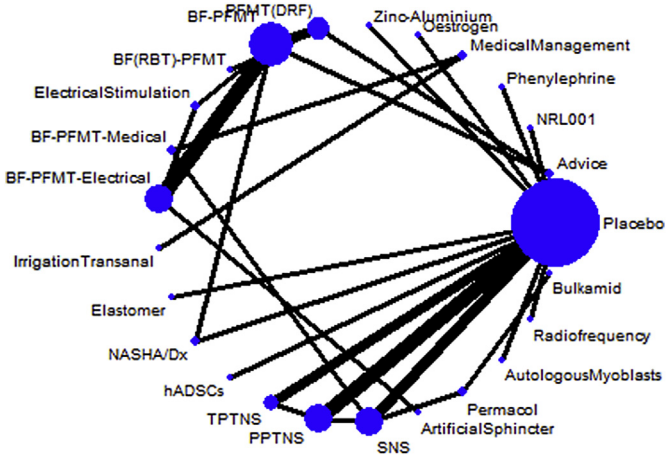

Fig. 3. Network plot for incontinence score, similar network plots were produced for each outcome of interest. Footnotes: circles represent the intervention as a node in the network; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison. BF = Biofeedback, RBT = Rectal Balloon Training, PFMT = Pelvic Floor Muscle Training, DRF = Digital Rectal Feedback, TPTNS = Transcutaneous Posterior Tibial Nerve Stimulation, NRL001 = 1R,2S-methoxamine hydrochloride, SNS = Sacral Nerve Stimulation, PPTNS = Percutaneous Posterior Tibial Nerve Stimulation, NASHA/Dx = Injection of Non-Animal Stabilized Hyaluronic Acid/Dextranomer, hADSCs = human adipose derived stem cells.

that injection of NASHA/Dx resulted in more patients with ≥50% reduction in FI episodes compared to placebo.

3.7. Anorectal manometry

Twelve trials reporting on 855 participants were included in the analysis for evaluating the effect of 12 treatments on resting anorectal pressure. On pairwise comparisons, no treatment demonstrated a superiority with regards to improvement in resting pressure. Similarly, a network meta-analysis reporting on four trials (256 participants; 6 treatments) highlighted no significant differences in maximum resting pressure between treatments during pairwise comparisons.

Seven trials reporting on 483 participants were included in the network meta-analysis for evaluating the effect of seven treatments on squeeze pressure. On pairwise comparisons, no treatment demonstrated a superiority with regards to improvement in squeeze pressure. Similarly, a network meta-analysis reporting on four trials (256 participants; 6 treatments) found no significant differences in maximum squeeze pressure between treatments during pairwise comparisons.

4. Discussion

The current network meta-analysis found that no treatment persistently improved the outcomes of interest and no treatment ranked best with high probability for any outcome. In addition, many of the included treatments for FI, including commonly used treatments such as biofeedback or pelvic floor muscle training or medical management, did not significantly benefit patients compared to placebo. Although the current study found no significant improvement with many of the treatments for FI, often in the clinical setting patients report improvement in symptoms. The review findings may suggest that there is an element of placebo effect in the mechanism of many of the current treatments for FI. A placebo effect cannot be discounted and RCTs comparing treatments for FI have demonstrated statistically significant improvements in incontinence scores in both the treatment group and the group of patients receiving placebo intervention [32]. On the other hand, faecal incontinence is a relatively objective issue, and patients may have improved anal manometry after treatment compared to control which is an objective measured parameter, despite the possibility of no improvement in patient symptoms. The management of FI is multifactorial and modifying one of these parameters may allow improvement in symptoms. For example, the relationship between the therapist and patient may influence treatment outcomes [28,32,37], and patients may have FI symptoms associated with alterations in their emotional status [61]. FI may be associated with worsening depression or anxiety; hence by improving their psychological status both the quality of life of sufferers together with their symptoms of FI may improve [62].

This network meta-analysis found that SNS improved the incontinence score and the FIQL lifestyle, coping, and embarrassment domains. A previous standard pairwise meta-analysis based on 34 studies suggested that SNS resulted in significantly improved incontinence scores, improved ability to defer defecation, improvement in most SF-36 and FIQL domains, and improved mean anal pressures [49]. The reported complication rate was 15% for permanent SNS, with 3% resulting in permanent explantation [49]. Overall, previous studies have demonstrated a persistent clinical efficacy with SNS, with low morbidity rate on long-term follow-up [44,63]. As the results for surgical repair for FI show deterioration during a 5-year follow-up, SNS has been suggested as a valid alternative or an adjunct to surgical repair in the treatment of FI in patients presenting with a sphincter lesion [64]. The current review also demonstrated an improvement in the FIQL embarrassment domain with TPTNS. A previous standard meta-analysis demonstrated significant improvement with SNS compared to PPTNS in the Wexner score, episodes of FI per week, and in the FIQL coping and depression domains [48]. A single-blinded RCT including comparing PPTNS versus TPTNS versus sham transcutaneous found that patients undergoing PPTNS had a greater reduction in the number of incontinence episodes and were able to defer defecation for a longer interval than those undergoing transcutaneous and sham stimulation [16]. On the other hand, the results from the multicentre, double-blind, randomized, controlled CONFIDeNT trial reported no significant clinical benefit of PPTNS over sham electrical stimulation [21].

Although study protocols exist [65], there is a paucity of RCTs comparing neuromodulation to other surgical treatments. A non-randomized prospective comparative study suggested that magnetic anal sphincter was as effective as SNS in improving continence and quality of life, with similar morbidity [66]. The present network meta-analysis enabled treatment comparisons and found that ABS improved incontinence scores compared to placebo, medical management, BF-PFMT plus medical management, transanal irrigation, elastomer implants, and PPTNS (but no difference compared to SNS), and ranked best with 81.7% probability for this outcome. Although the current review did not identify a significant difference in adverse events, several safety issues have been reported with ABS, including high incidence of surgical revision and explantation of ABS, and high rates of adverse events owing to infection, device malfunction, erosion/ulceration and pain [67,68]. Possible indications for ABS implantation include end-stage severe FI in patients with extensive anal sphincter loss, congenital anorectal malformation, or perineal colostomy [69]. In patients with no sphincter defect or with a defect of more than 120° of the anal circumference, SNS nerve stimulation may be the proposed surgical treatment [67].

Adult stem cell therapy is a promising non-invasive treatment option for FI by regenerating damaged sphincter [7]. The current network meta-analysis assessed the efficacy of intrasphincteric injections of autologous myoblasts compared to other treatments for FI, and has only demonstrated an improvement in the FIQL depression domain compared to placebo. Another increasingly used minimally invasive treatment for FI is the transanal submucosal injection of a bulking agent in the anal canal [14,17,70]. The present review assessed the efficacy of NASHA/Dx injections compared to other FI treatments, and found only a higher number of patients with 50% or greater reduction in the number of episodes of FI per week compared to placebo. Similarly, a

Table 2
The treatments included in the network meta-analysis for each outcome of interest. Footnotes: CMC = Carboxymethylcellulose, BF = Biofeedback, RBT = Rectal Balloon Training, PFMT = Pelvic Floor Muscle Training, DRF- Digital Rectal Feedback, TPTNS = Transcutaneous Posterior Tibial Nerve Stimulation, TPFR = Total Pelvic Floor Repair, NRL001 = 1R,2S-methoxamine hydrochloride, SNS = Sacral Nerve Stimulation, PPTNS = Percutaneous Posterior Tibial Nerve Stimulation, NASHA/Dx = Injection of Non-Animal Stabilized Hyaluronic Acid/Dextranomer, FI = Faecal Incontinence, Freq = Frequency, FIQL = Faecal incontinence quality of life, SP = Squeeze Pressure, RP = Resting Pressure, MSP = Maximum Squeeze Pressure, MRP = Maximum Resting Pressure.

Treatment	Network meta-analysis										
	Adverse Events	FIQL-Lifestyle domain	FIQL-Coping domain	FIQL-Depression domain	FIQL-Embarrassment domain	FI score	FI frequency	50% reduction in FI	RP	MRP	SP	MSP
Placebo	•	•	•	•	•	•	•	•	•			
Advice	•					•			•			
CMC	•						•					
Gum Arabic	•						•					
Psyllium	•						•					
Clonidine	•	•	•	•	•			•				
Topical NRL001	•					•	•					
Topical Phenylephrine	•					•						
Loperamide	•						•					
Medical management (antidiarrheals and laxatives)	•					•			•		•	
Topical oestrogen	•	•	•	•	•	•						
Zinc-Aluminium Ointment	•	•	•	•	•	•						
PFMT	•											
PFMT (with DRF)	•					•			•		•	
BF-PFMT	•	•	•	•	•	•			•		•	
BF(RBT)—PFMT	•					•			•			
Electrical Stimulation	•					•			•		•	
BF-PFMT and medical management	•	•	•	•	•	•	•					
BF-PFMT-electrical stimulation	•	•	•	•	•	•			•		•	
Transanal irrigation	•					•						
Elastomer Implant	•	•	•	•	•	•						
NASHA/Dx injection	•	•	•	•	•	•		•	•		•	
TPTNS	•	•	•	•	•	•	•	•	•			
PPTNS	•	•	•	•	•	•	•	•	•			
SNS	•	•	•	•	•	•	•					
Artificial Bowel Sphincter	•					•						
Human adipose derived stem cells	•					•						
Permacol	•	•	•	•	•	•						
Autologous Myoblasts	•	•	•	•	•	•			•		•	
Radiofrequency	•					•						
Bulkamid	•					•						
Anal plug and electrical stimulation										•		•
Anterior Levatorplasty										•		•
Post anal repair										•		•
Total Pelvic Floor Repair										•		•
Total Pelvic Floor Repair and Internal Sphincter Plication										•		•
Gluteus Maximus Transposition										•		•

randomized, double-blind, sham-controlled trial, demonstrated a significantly higher proportion of patients after NASHA/Dx injections with 50% or more reduction in FI episodes compared to placebo [17,70]. This network meta-analysis has also found that zinc-aluminium ointment improved the incontinence score and all domains of the FIQL compared to placebo and other treatments. The mechanism of action is unclear, but there is evidence that some metals, such as aluminium, can increase the contraction of smooth muscle [33,71]. Nevertheless, this is based on the results of only one randomized double-blinded trial [33], of small size and with inadequate follow-up [33,71].

Despite the extensive statistical analysis of the current study, it is still difficult to suggest a simple unifying treatment algorithm for all patients suffering with FI due to symptoms variation and significant interrelation between the different treatments and outcomes. For example, as shown in Table 4 one treatment may have the highest probability for being the best treatment for adverse events or FIQL-Coping, but also have the highest probability for being the worst treatment for incontinence score. An attempt is made to propose an algorithm (Fig. 4) for the management of patients with faecal incontinence based on the results of the current network meta-analysis and the treatments which are widely available for FI. It is suggested to first attempt non-invasive treatments for FI, with associated low risk of adverse events, such as biofeedback-pelvic floor muscle training in combination with medical management including antidiarrheal medications (e.g. loperamide), laxatives, bulking agents (e.g. fibre), rectal irrigation, and anal plug. If symptoms of FI persist, it is suggested to proceed with more invasive treatments, such as electrical stimulation, SNS, TPTNS, PPTNS, and bulking agent injection such as NASHA/Dx. If there is a sphincter defect less than 120°, consider overlapping sphincteroplasty. ABS was not included in the algorithm due to the

Table 3

Statistically significant pairwise odds ratios and mean differences of the different treatment comparisons for all outcomes of interest. Footnotes: OR = odds ratio, MD = mean difference, (95% credible intervals), FI = faecal incontinence, FIQL = faecal incontinence quality of life, ABS = artificial bowel sphincter, CMC = Carboxymethylcellulose, BF = Biofeedback, RBT = Rectal Balloon Training, PFMT = Pelvic Floor Muscle Training, DRF = Digital Rectal Feedback, TPTNS = Transcutaneous Posterior Tibial Nerve Stimulation, TPFR = Total Pelvic Floor Repair, NRL001 = 1R,2S-methoxamine hydrochloride, SNS = Sacral Nerve Stimulation, PPTNS = Percutaneous Posterior Tibial Nerve Stimulation, NASHA/Dx = Injection of Non-Animal Stabilized Hyaluronic Acid/Dextranomer.

Frequency of FI	No significant differences between treatments
Resting pressure	No significant differences between treatments
Maximum resting pressure	No significant differences between treatments
Squeeze pressure	No significant differences between treatments
Maximum squeeze pressure	No significant differences between treatments
Adverse events	Radiofrequency worse compared to: placebo (OR 8.52; 95% CI 2.39 to 30.47), NRL001 (OR 6.43; 95% CI 1.69 to 24.5)
50% reduction in FI frequency	NASHA/Dx better compared to placebo (OR 0.41; 95% CI 0.22 to 0.77)
FIQL lifestyle	SNS better compared to placebo (MD -0.69; 95% CI -1.32 to −0.05) Zinc-aluminium better compared to: placebo (MD -1.04; 95% CI -1.44 to −0.64), clonidine (MD -1.14; 95% CI -2.26 to −0.02), BF-PFMT (MD 1.06; 95% CI 0.14 to 1.98), BF-PFMT plus medical management (MD 1.22; 95% CI 0.24 to 2.21), BF-PFMT plus electrical stimulation (MD 1.07; 95% CI 0.12 to 2.02), elastomer implants (MD 1.54; 95% CI 0.42 to 2.66), NASHA/Dx (MD 0.72; 95% CI 0.07 to 1.36), TPTNS (MD 1.04; 95% CI 0.49 to 1.58), PPTNS (MD 1.06; 95% CI 0.52 to 1.6), Permacol (MD 1.25; 95% CI 0.41 to 2.1)
FIQL coping	SNS better compared to placebo (MD -0.85; 95% CI -1.59 to −0.11) Zinc-aluminium better compared to: placebo (MD -0.73; 95% CI -1.11 to −0.35), TPTNS (MD 0.63; 95% CI 0.16 to 1.11), PPTNS (MD 0.68; 95% CI 0.15 to 1.22), Permacol (MD 0.93; 95% CI 0.01 to 1.85)
FIQL depression	Autologous myoblasts better compared to placebo (MD -0.6; 95% CI -1.04 to −0.15), PPTNS (MD -0.64; 95% CI -1.19 to −0.1) Zinc-aluminium better compared to: placebo (MD -0.76; 95% CI -1.14 to −0.38), BF-PFMT (MD 0.88; 95% CI 0.1 to 1.66), BF-PFMT plus electrical stimulation (MD 0.86; 95% CI 0.04 to 1.67), NASHA/Dx (MD 0.59; 95% CI 0.09 to 1.09), TPTNS (MD 0.59; 95% CI 0.02 to 1.16), PPTNS (MD 0.81; 95% CI 0.31 to 1.3), Permacol (MD 0.91; 95% CI 0.18 to 1.65)
FIQL embarrassment	SNS better compared to: placebo (MD -1.13; 95% CI -1.92 to −0.33), PPTNS (MD -1; 95% CI -1.91 to −0.1), autologous myoblasts (MD 1.43; 95% CI 0.41 to 2.45) TPTNS better compared to placebo (MD -0.29; 95% CI -0.54 to −0.05) Zinc-aluminium better compared to: placebo (MD -0.72; 95% CI -1.13 to −0.31), autologous myoblasts (MD 1.02; 95% CI 0.27 to 1.78)
Incontinence score	SNS better compared to placebo (MD -4.06; 95% CI -7.16 to −0.95), NRL001 (MD -3.95; 95% CI -7.28 to −0.62), medical management (MD -12.69; 95% CI -19.59 to −5.79), BF-PFMT plus medical management (MD -13.68; 95% CI -19.66 to −7.71), transanal irrigation (MD -8.9; 95% CI -17.22 to −0.58), Permacol (MD 7.39; 95% CI 2.47 to 12.31), Bulkamid (MD 5.73; 95% CI 0.13 to 11.34) ABS better compared to: placebo (MD -13.84; 95% CI -26.73 to −0.95), advice alone (MD -14.96; 95% CI -29.68 to −0.24), NRL001 (MD -13.73; 95% CI -26.68 to −0.79), medical management (MD -22.48; 95% CI -36.77 to −8.19), BF-PFMT plus medical management (MD -23.47; 95% CI -37.33 to −9.6), transanal irrigation (MD -18.69; 95% CI -33.71 to −3.66), elastomer implants (MD -14.87; 95% CI -29.34 to −0.4), NASHA/Dx (MD -13.63; 95% CI -26.92 to −0.33), PPTNS (MD -13.22; 95% CI -26.22 to −0.22), Permacol (MD 17.18; 95% CI 3.73 to 30.62), Bulkamid (MD 15.52; 95% CI 1.81 to 29.23) Zinc-aluminium better compared to: placebo (MD -4.49; 95% CI -8.03 to −0.95), NRL001 (MD -4.39; 95% CI -8.12 to −0.65), medical management (MD -13.13; 95% CI -20.24 to −6.02), BF-PFMT plus medical management (MD 14.12; 95% CI 7.91 to 20.33), transanal irrigation (MD 9.34; 95% CI 0.85 to 17.83), Permacol (MD 7.83; 95% CI 2.62 to 13.03), Bulkamid (MD 6.17; 95% CI 0.31 to 12.03) Medical management worse compared to: placebo (MD 8.64; 95% CI 2.47 to 14.8), NRL001 (MD 8.74; 95% CI 2.46 to 15.02), phenylephrine (MD 9.55; 95% CI 0.04 to 19.05), oestrogen (MD -10.64; 95% CI -17.32 to −3.96), PFMT-DRF (MD -8.66; 95% CI -17.32 to −0.01), BF-PFMT (MD -9.61; 95% CI -17.56 to −1.67), electrical stimulation (MD -11.7; 95% CI -20.34 to −3.07), BF-PFMT plus electrical stimulation (MD -11.36; 95% CI -19.7 to −3.03), NASHA/Dx (MD -8.85; 95% CI -15.82 to −1.88), PPTNS (MD -9.26; 95% CI -15.65 to −2.87), TPTNS (MD -9.72; 95% CI -16.72 to −2.72), autologous myoblasts (MD -11.12; 95% CI -17.89 to −4.35) BF-PFMT plus medical management worse compared to: placebo (MD 9.63; 95% CI 4.52 to 14.73), advice alone (MD 9.14; 95% CI 0.27 to 18.01), NRL001 (MD 9.73; 95% CI 4.49 to 14.98), phenylephrine (MD 10.54; 95% CI 1.68 to 19.39), oestrogen (MD 11.63; 95% CI 5.91 to 17.35), PFMT-DRF (MD 9.66; 95% CI 1.72 to 17.59), BF-PFMT (MD 10.61; 95% CI 3.45 to 17.76), BF (RBT) plus PFMT (MD 10.51; 95% CI 1.25 to 19.78), electrical stimulation (MD 12.7; 95% CI 4.78 to 20.61), BF-PFMT plus electrical stimulation (MD -12.36; 95% CI -19.94 to −4.77), elastomer (MD -8.6; 95% CI -16.92 to −0.27), NASHA/Dx (MD -9.84; 95% CI -15.9 to −3.79), PPTNS (MD -10.25; 95% CI -15.63 to −4.87), TPTNS (MD -10.71; 95% CI -16.8 to −4.63), autologous myoblasts (MD -12.12; 95% CI -17.94 to −6.29), Bulkamid (MD -7.95; 95% CI -14.87 to −1.03) Permacol worse compared to: topical oestrogen (MD 5.34; 95% CI 0.74 to 9.94), autologous myoblasts (MD 15.52; 95% CI 1.81 to 29.23)

Table 4

Treatments with the highest probability of ranking best or worst for the outcomes of interest.

Outcome measure	Best (%)	Worst (%)
Adverse events	Biofeedback-pelvic floor muscle training plus electrical stimulation (18.7%)	Phenylephrine (15.7%)
FIQL-Lifestyle	Autologous myoblasts (45.9%)	Elastomer Implants (39.4%)
FIQL-Coping	Biofeedback-pelvic floor muscle training plus medical management (26.5%)	Elastomer Implants (31.9%)
FIQL-Depression	Zinc-aluminium ointment (51.7%)	Elastomer Implants (28.0%)
FIQL-Embarrassment	Sacral nerve stimulation (47.9%)	Topical oestrogen ointment (23.2%)
Incontinence score	Artificial bowel sphincters (81.7%)	Biofeedback-pelvic floor muscle training plus medical management (60.9%)
FI episodes per week	Loperamide (38.3%)	Carboxymethylcellulose (32.5%)
50% reduction in FI episodes	Injection of Non-Animal Stabilized Hyaluronic Acid/Dextranomer (54.5%)	Transcutaneous Posterior Tibial Nerve Stimulation (46.5%)
Resting pressure	Electrical Stimulation (34.0%)	Medical Management (antidiarrheal medications and laxatives) (25.1%)
Maximum resting pressure	Anal plug plus electrical stimulation (53.7%)	Post anal repair (40.0%)
Squeeze pressure	Medical Management (antidiarrheal medications and laxatives) (35.0%)	Autologous myoblasts (24.3%)
Maximum squeeze pressure	Total pelvic floor repair and internal sphincter plication (71.7%)	Post anal repair (65.2%)

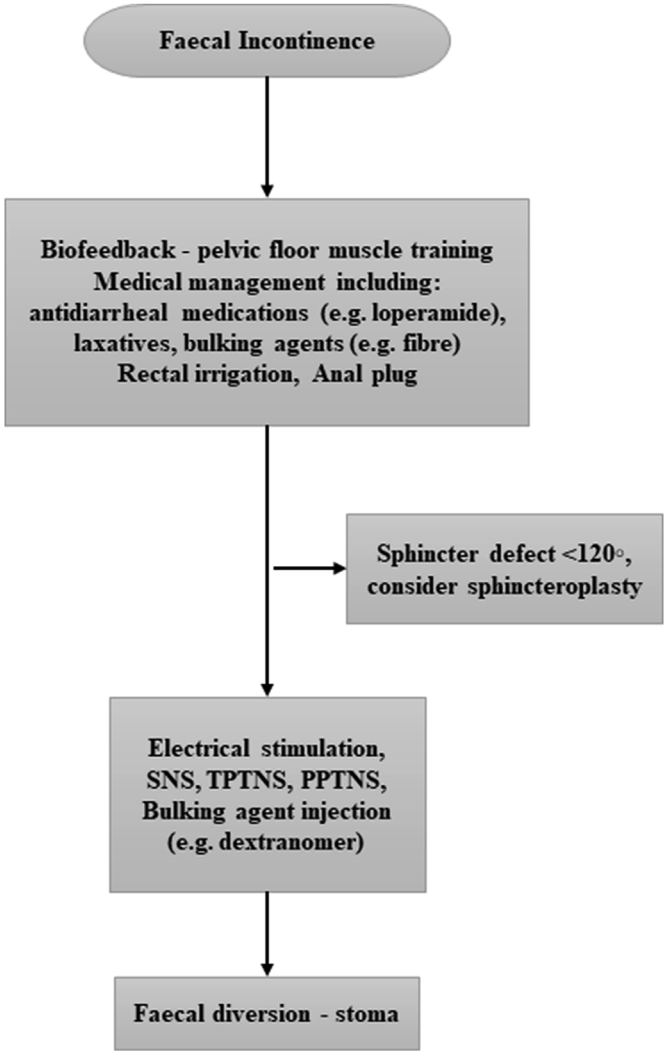

Fig. 4. A proposed algorithm for the management of patients with faecal incontinence. Footnotes: TPTNS = Transcutaneous Posterior Tibial Nerve Stimulation, SNS = Sacral Nerve Stimulation, PPTNS = Percutaneous Posterior Tibial Nerve Stimulation.

significant risks of adverse events. If all of the above fail and FI continues to significantly affect the patient's quality of life, then last resort treatment would be faecal diversion with a stoma.

This review is the first evidence-based systematic approach, which highlighted the highest quality of evidence in the form of RCTs and provided an up-to-date insight into the management options for FI. Placebo was the most frequent comparator for the network meta-analyses, but it should be noted that the mode of "placebo" was variable between studies. Furthermore, there is variation between studies in the inclusion criteria, with some studies requiring patients to have liquid/stool incontinence [6,8], and other studies selecting patients based on measures such Wexner score [36,38,39], or Vaizey score [14]. Moreover, comparing treatments for FI can be complicated by the longitudinal sequence of the treatments provided to patients. Also, there is variation between studies in the delivery of treatments such as BF and PFMT, with variation in the number of sessions, duration and intensity. A wide range of outcome measures were used by studies to report treatment effect. To permit comparison between FI treatments, it is imperative to standardize the inclusion criteria, methodology, follow-up period, and outcome measures across studies in the field.

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Author contribution

- Constantinos Simillis: conception and design of the study, literature search, acquisition of data, data analysis, interpretation of data, drafting the article, final approval of the article, agreement to be accountable for all aspects of the work.
- Nikhil Lal: literature search, acquisition of data, data analysis, drafting the article, final approval of the article, agreement to be accountable for all aspects of the work.
- Gianluca Pellino: acquisition of data, data analysis, drafting the article, final approval of the article, agreement to be accountable for all aspects of the work.
- Daniel Baird: conception and design of the study, acquisition of data, interpretation of data, article revision, final approval of the article, agreement to be accountable for all aspects of the work.
- Stella Nikolaou: conception and design of the study, acquisition of data, interpretation of data, article revision, final approval of the article, agreement to be accountable for all aspects of the work.
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- Jason J Smith: conception and design of the study, interpretation of data, article revision, final approval of the article, agreement to be accountable for all aspects of the work.
- Paris P Tekkis: conception and design of the study, interpretation of data, article revision, final approval of the article, agreement to be accountable for all aspects of the work.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix ASupplementary data

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