REVIEW

Treatment of Fecal Incontinence: State of the Science Summary for the National Institute of Diabetes and Digestive and Kidney Diseases Workshop

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This is the second of a two-part summary of a National Institutes of Health conference on fecal incontinence (FI) that summarizes current treatments and identifies research priorities. Conservative medical management consisting of patient education, fiber supplements or antidiarrheals, behavioral techniques such as scheduled toileting, and pelvic floor exercises restores continence in up to 25% of patients. Biofeedback, often recommended as first-line treatment after conservative management fails, produces satisfaction with treatment in up to 76% and continence in 55%; however, outcomes depend on the skill of the therapist, and some trials are less favorable. Electrical stimulation of the anal mucosa is ineffective, but continuous electrical pulsing of sacral nerves produces a ≥50% reduction in FI frequency in a median 73% of patients. Tibial nerve electrical stimulation with needle electrodes is promising but remains unproven. Sphincteroplasty produces short-term clinical improvement in a median 67%, but 5-year outcomes are poor. Injecting an inert bulking agent around the anal canal led to ≥50% reductions of FI in up to 53% of patients. Colostomy is used as a last resort because of adverse effects on quality of life. Several new devices are under investigation but not yet approved. FI researchers identify the following priorities for future research: (1) trials comparing the effectiveness, safety, and cost of current therapies; (2) studies addressing barriers to consulting for care; and (3) translational research on regenerative medicine. Unmet patient needs include FI in special populations (e.g., neurological disorders and nursing home residents) and improvements in behavioral treatments.

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INTRODUCTION

This is the second of two articles summarizing the proceedings of a conference held at the National Institutes of Health on 19–20 August 2013, which was titled "Developing a Clinical Research Agenda for Fecal Incontinence". Day 1 of the conference addressed the definition, pathophysiology, epidemiology, and impact of fecal incontinence (FI). It also reviewed measurement instruments for the severity and quality of life impact of FI, and proposed a classification scheme to guide diagnostic assessment. The first day of the conference was summarized separately (1).

Day 2 of the conference included expert reviews of the current state of the art, with respect to behavioral, medical, and surgical treatments for FI. These reviews were followed by discussions of the challenges that are unique to the design of clinical trials for behavioral and surgical interventions, and recommendations for the design of future clinical trials. The conference concluded with an open session in which conference attendees were invited to identify other knowledge gaps and research priorities. A survey questionnaire soliciting information on clinical research priorities was also distributed to FI investigators before the conference and to conference attendees on Day 2; the findings of these surveys are summarized here.

SELF-MANAGEMENT

Epidemiological studies suggest that ~70% of patients with FI have not consulted a physician or other health-care providers (2,3). The mainstay of self-management is the use of absorbent

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pads or protective garments, often supplemented by diet restriction. There is no published literature on effectiveness or satisfaction with these self-management techniques. Research is needed to determine whether patients with small volume fecal soiling may be adequately managed and satisfied with absorbent pads.

CONSERVATIVE MEDICAL MANAGEMENT

Conservative medical management may include (1) patient education regarding the physiology of continence and the causes of FI; (2) normalization of stool consistency by dietary fiber supplements or antidiarrheal medication or laxatives as appropriate; (3) behavioral techniques such as scheduled toileting attempts and prevention strategies (e.g., "squeeze before coughing or lifting"); and/or (4) daily exercises to strengthen pelvic floor muscles (**Box 1**). The evidence for each of the components of conservative management is as follows:

Box 1. Noninvasive therapies

- Fiber supplements and antidiarrheal drugs for diarrhea-associated FI
- Laxatives, enemas, or suppositories for constipation-associated FI
- Pelvic floor exercises
- Biofeedback
- Electrical stimulation of anal mucosa

Patient education

There is no objective evidence that education makes an independent contribution to improvement in FI (4). However, expert opinion holds that it is an important component of medical management, and websites (e.g., www.digestive.niddk.nih.gov/ddiseases/pubs/fecalincontinence/) and patient brochures have been developed to meet this need.

Fiber, antidiarrheal medications, and laxatives

Fiber is frequently recommended to normalize stool consistency, and a small randomized controlled trial (RCT) showed that fiber supplementation decreased diarrhea-associated FI (5). There is no documented evidence that fiber supplements benefit patients with constipation-associated FI, although clinicians often use fiber for this indication. Systematic reviews indicate that antidiarrheal drugs improve diarrhea-associated FI more than placebo, and loperamide is more effective compared with diphenoxylate (6,7); however, the evidence is of poor quality. Cholestyramine 2–6 g daily was associated with improvements in diarrhea-associated FI in an uncontrolled trial (8). Clonidine, an alpha 2 adrenoreceptor agonist, was tested in a large RCT that enrolled patients with FI, irrespective of whether they had diarrhea; at a dose of 0.1 mg twice daily, clonidine decreased diarrhea episodes but did not significantly decrease FI frequency (9). Further research on clonidine is needed. Topical phenylephrine and oral valproate sodium, which are drugs that increase smooth muscle tone, have been tested in patients with FI associated with decreased internal anal sphincter resting pressure (principally, these are patients with ileal pouch procedures), and they yield a statistically significant but weak improvement in bowel control (7). The laxative lactulose benefits some nursing home residents with FI associated with fecal impaction (7). The evidence base for specific treatment modalities is summarized in **Table 1**.

Table 1. Evidence-based assessment and recommendation for specific therapies

Treatment modality	Level of evidence[a]	Recommendation grade[b]
Pharmacological		
Loperamide	II	B
Diphenoxylate/atropine	II	B
Lactulose	II	C
Fiber supplements	II	B
Amitriptyline	II	B
Clonidine	II	C
Cholestyramine	III	C
Topical therapy		
Zinc aluminum	II	B
Estrogen	II	B
Phenylephrine	II	C
Biofeedback	I	A
Surgical treatment		
Sacral nerve stimulation	II	B
Sphincteroplasty	II	B
Colostomy	III	B
Novel therapies		
Tibial electrical stimulation	I	C
Dextranomer Injection	I	B

[a]Evidence is graded level I if at least one properly randomized controlled trial is available, level II if well-designed cohort or retrospective case–control studies support the recommendation, and level III if the evidence consists of expert opinion or descriptive studies and case reports.

[b]Recommendations are graded A if strongly recommended, grade B if recommended, grade C if the balance of evidence does not allow a recommendation for or against to be made, and grade D if the evidence suggests that the harms outweigh the benefits (71).

Behavioral training

Recommendations to patients that they attempt defecation at specific times of the day or try to prevent FI by techniques such as squeezing before activities that are likely to increase intra-abdominal pressure have not been tested for their independent contributions to continence.

Pelvic floor exercises

These exercises are nearly always recommended to patients with FI, but there is little consensus on how they should be taught. There are no known RCTs that test the efficacy of pelvic floor exercises alone, although pre-post comparisons suggest that they are effective (10). In some recent studies, pelvic floor exercises were

taught by a health-care provider during a digital rectal examination, and reductions in FI from baseline were comparable to those achieved with biofeedback training using electronic devices (11,12). However, there are no RCTs comparing exercise training by digital rectal examination to verbal instructions only.

In clinical practice, conservative medical management usually includes the four components listed above. There are no RCTs comparing multicomponent medical management to no-treatment, but there are prospective observational studies that provide a basis for estimating the expected reduction from baseline: a 1-month conservative management intervention incorporating patient education, normalization of stool consistency with fiber and medication, and behavioral strategies (but no pelvic floor exercises) yielded a 60% reduction in the frequency of FI and reported adequate relief of FI in 21% (10). These improvements were maintained in at least 2/3 of patients for 12 months. In another study, a similar combination of patient education, diet, and drug interventions to normalize stool consistency, and behavioral strategies was associated with a self-report of "improved" FI status in ~55% of patients but no patients reported "cure" (11).

BIOFEEDBACK

Biofeedback involves the use of electronic or mechanical devices to provide augmented awareness of physiological responses to patients and their therapists to facilitate neuromuscular retraining. The goals are to correct the most common physiological deficits that contribute to FI by (1) improving the strength and isolation of pelvic floor muscle contractions, (2) improving the ability to sense and contract pelvic floor muscles in response to weak distentions of the rectum; and/or (3) improving the ability to tolerate larger rectal distentions without experiencing uncontrollable urge sensations. Following biofeedback strength training, anal squeeze pressures increased, and inappropriate abdominal wall muscle contractions decreased in some (10) but not in all studies (13). In patients with reduced rectal sensation, biofeedback therapy improves rectal sensation (14,15), and shortens the latency between rectal distention and contraction of the external anal sphincter (16). There are no published studies on the outcomes of urge resistance training for FI.

RCTs of biofeedback have yielded inconsistent results: two large studies (11,12) showed no benefit for biofeedback compared with pelvic floor exercises taught by digital rectal exam, whereas a third study (10) showed a clear superiority for biofeedback compared with pelvic floor exercises taught verbally. In the third study, which had the strongest design, patients with severe FI (at least weekly solid or liquid stool accidents) first underwent a 1-month screening period on conservative management, and patients who achieved adequate relief were excluded from further participation. The remaining 107 patients underwent biofeedback training by an experienced biofeedback therapist during six biweekly sessions, and were reassessed at 3-month and 12-month- follow-up. In the intent-to-treat analysis, 76% of biofeedback patients vs. 41% of pelvic floor exercise patients reported adequate relief at 3-month follow-up. Results were well maintained at 12 months in this and in an independent, uncontrolled study (17). Biofeedback is recommended for the treatment of FI by the American College of Gastroenterology (18) and the American Gastroenterological Association (19). Further research is needed to standardize the treatment protocols and the training of biofeedback therapists.

ELECTRICAL STIMULATION

Electrical stimulation from anal electrodes

When used as the sole therapy, electrical stimulation of the anus through the skin or mucosa does not appear to be effective (20,21). However, one group reported that a complex protocol combining anal electri)cal stimulation with electromyographic biofeedback was superior to either electrical stimulation (22) alone or biofeedback (23) alone. In this protocol, a pelvic floor electromyographic response above a minimum threshold triggered an electrical pulse that augmented the pelvic floor muscle contraction. Six to nine months of twice daily exercises combined with electrical stimulation at home were required to produce significant clinical improvements in FI.

Sacral nerve stimulation (neuromodulation)

Sacral nerve stimulation (SNS) is a type of electrical stimulation in which electrodes are inserted adjacent to sacral nerves and continuously pulsed by a battery-operated stimulator. The procedure is performed in two phases: (1) in the first visit, percutaneous electrodes are inserted into the sacral foramina to identify an electrode location that causes a contraction of the external anal sphincter. These electrodes are connected to an external electrical stimulator, and stimulation is applied for 2–3 weeks to determine whether there is at least a 50% reduction in FI frequency. (2) If the 2- to 3-week trial is successful, the battery-operated stimulator is permanently implanted beneath the skin. Most studies of SNS in FI have been uncontrolled. In the pivotal US multicenter trial, 90% of 133 patients proceeded from temporary to permanent stimulation (24). Five-year follow-up was available in 76 of 120 patients (63%); 36% reported complete continence and 89% were deemed a therapeutic success (25). In one crossover study of 34 patients, the number of episodes of FI declined by 90% during stimulation vs. 76% without stimulation (26). Small (<30 patients) RCTs comparing SNS with no stimulation or medical therapy support its efficacy (26–28), but most of these trials have been performed in patients with structurally intact and innervated sphincters; the median proportion of such patients achieving at least a 50% reduction in FI on an intent-to-treat basis is 73% (29). Limited data that are available from patients with an external sphincter defect suggest that SNS is also effective in this group, although outcomes are less predictable, and effect sizes are smaller (30). Improvements in continence with continuous SNS are maintained for at least 5 years (31,32). Batteries must be replaced after ~7 years (33). The most common adverse events are pain and infection at the insertion site, which occur in 3% (29) to 11% (34). These data demonstrate that SNS is an effective surgical option for selected patients with FI, but sham controlled, prospec-

tive RCTs that are not restricted to patients with intact sphincters are still needed. The mechanism of action of SNS effects on FI is unknown (35).

Three studies (36–38) tested the effects of stimulating sacral nerves using skin-surface electrodes. Patients used battery-operated electrical stimulators for 2–12 h each day for 1–3 months. The median proportion of patients reporting at least a 50% reduction in FI frequency was 70% (38), which is comparable to the results reported with implanted stimulators. However, these small uncontrolled studies did not account for placebo effects.

Tibial nerve stimulation

Posterior tibial nerve stimulation is carried out either using a skin-surface electrode placed over the nerve in a position posterior and superior to the medial malleolus (transcutaneous stimulation) or with a needle inserted through the skin in the same area (percutaneous stimulation). Thomas *et al.* (39) reviewed 13 studies but noted that methods varied, making comparisons difficult. Although outcomes were mixed, 62–82% of patients reported at least a 50% reduction in frequency of FI. A large multicenter RCT found that transcutaneous stimulation was not significantly better than sham stimulation (40), and a study that compared percutaneous with transcutaneous stimulation showed that percutaneous stimulation was significantly better (41) (**Box 2**).

Box 2. Invasive therapies

- Sacral nerve stimulation (neurostimulation)
- Injectable bulking agents
- Sphincteroplasty and artificial sphincter
- Colostomy

SPHINCTEROPLASTY AND POST-ANAL REPAIR

When sphincter injuries are recognized during birth, they are repaired immediately by overlapping or juxtaposing the ends of the separated sphincter and suturing them. These acute repairs are not reported in the literature on treatment of FI; rather the results of secondary sphincteroplasties, performed when the woman presents with FI and shows evidence of internal or external sphincter separation, are reported. In the short term, a median 67% of patients are described as having "good" or "excellent" outcome following these secondary repairs (42). However, follow-up at 5 years shows that the median proportion rated "good" or "excellent" at that point is 51% (43).

Post-anal repair is a surgical procedure in which the puborectalis is plicated with the objective of restoring the anorectal angle and lengthening the anal canal. A total pelvic repair involves a combination of puborectalis plication with sphincteroplasty. For post-anal repair, published series show continence in a median 27% and "improvement" in a median 74%. A small RCT comparing post-anal repair, anterior levator plication (sphincteroplasty), and total pelvic floor repair found a significant advantage for total pelvic repair (44), but subsequent experience has not supported its efficacy, and post-anal repair has been largely abandoned (45).

OTHER SURGICAL PROCEDURES

Graciloplasty

The gracilis muscle from one leg is freed at its distal end and wrapped around the anal canal to create an innervated neosphincter. In dynamic graciloplasty, an electrical stimulator is implanted to continuously pulse this neosphincter (46). The median success rate for dynamic graciloplasty in published series is 67%, although the definition of success varies. Complication rates for this procedure are high and include obstructed defecation. This procedure has not gained traction, and the stimulator is not approved for use in the United States.

Radiofrequency lesions (SECCA)

Radiofrequency energy from a probe in the anal canal is used to create submucosal injuries in the distal rectum and anal canal, with the goal of causing scarring and increased resistance to stool passage. A multicenter prospective series of 50 patients with weekly FI at baseline yielded statistically significant but relatively small improvements in the Cleveland Clinic Florida Fecal Incontinence score from 13.5 to 11.1 and significant improvements on Fecal Incontinence Quality of Life scores (47). Complications included mucosal lesions in 2/50 and bleeding in a third patient. A subsequent publication (48) on a retrospective series showed long-term benefit in only 22% and noted that most patients underwent additional treatments.

INJECTION OF INERT BULKING AGENTS AROUND THE ANAL CANAL

Efforts to improve FI by injecting inert substances around the anal canal to increase resting anal canal pressure began in 1993 (49). There are several reviews (50–52). The types of substances injected have included silicone elastomers, carbon-coated zirconium beads, ceramic beads, and dextranomer microspheres (51). Until 2011, these trials provided no clear evidence of efficacy for the treatment of FI. However, a large multicenter RCT (53) from eight US and five European centers published in 2011 supports the efficacy for dextranomer injections compared with sham injections. In this study, patients were required to have a Cleveland Clinic Florida Incontinence Score of at least 10 (moderate severity) to be included, and patients with sphincter injuries were included unless the sphincter separation was complete. At 3-month follow-up, 52% of the dextranomer-injected patients had at least a 50% decrease in FI frequency, whereas only 31% of sham-treated patients achieved this. A follow-up study showed that these gains were stable for 36 months (54).

IMPLANTED DEVICES

Many devices for preventing or containing FI are in use or are under development. However, it is rare that devices are tested in RCTs because regulatory approval only requires evidence of safety. Once they are found to be safe and possibly effective, RCTs will be needed to compare these approaches with conservative medical management or other established treatments.

Thiersch ring

A permanent suture or other synthetic material encircles the anal canal to increase resistance to stool leakage. This procedure was originally developed to treat rectal prolapse but was tested in 33 patients with FI. Significant improvements in FI were seen, but in 13 patients the sutures had to be removed (3 permanently) because of erosion or infection (n=4) or device breakage (n=9).

Artificial bowel sphincter

An inflatable cuff surrounding the anal canal can be inflated using an implanted pump to prevent stool passage and deflated to permit defecation (55). For patients who retained the device at follow-up, Wexner incontinence scores decreased from 16 to 7. However, device erosions and infections caused revisions in half and explant in a quarter. Obstructed defecation is also seen in more than half of patients (55).

Magnetic beads

A band of magnetic beads fitted on an elastic band is inserted around the anal canal to increase the resting pressure in the anal canal. Straining separates the beads to permit defecation. A small uncontrolled series(56) showed ~90% improvement in FI frequency in five patients who retained the device for 6 months. Complications were few: 2/14 devices had to be removed. Other small studies showed success rates comparable to the artificial bowel sphincter(57) and SNS (58) but with less morbidity. This device has not yet been approved in the United States.

Mesh sling support of the puborectalis muscle

A mesh sling is inserted through small incisions lateral to the anus and tunneled beneath the puborectalis via a transobturator approach, with guidance from digital rectal examination. The trial evaluating this technique has been completed with long-term data being accrued, but results are not yet available.

DEVICES USED OUTSIDE THE BODY

Anal plugs

These have been reviewed (59). A variety of types have been tried, and most produce discomfort and are not tolerated. However, newer models made of softer material are under investigation. When patients are able to tolerate the devices, they report improvement in FI (**Box 3**).

Vaginally inserted balloon

This device consists of a silicone balloon that can be inserted into the vagina while deflated and then inflated with a detachable pump to a pressure sufficient to obstruct stool passage in the nearby rectum. A prospective uncontrolled study to evaluate the safety and efficacy has been completed with long-term data being accrued; data are not yet available.

Box 3. Emerging therapies

- Tibial nerve electrical stimulation
- Anal plug devices
- Mesh sling support for anorectal angle
- Vaginal balloon device

STOMAS

Colostomy or ileostomy prevents all instances of FI, although mucus may still leak if the patient retains their rectum. This treatment option is infrequently used because, in most surveys, patients with ostomies report poorer quality of life than controls (60,61). The greatest impact on quality of life is in social roles, and women experience greater impairments than men. In another survey in which patients were recruited through an advertisement in the magazine of the British Colostomy Association(62), the majority were positive about the stoma, and 84% said they would choose it again. Ascertainment bias may contribute to the differences between these studies.

The Malone antegrade colonic enema is a technique used frequently in children with chronic constipation and/or FI (63,64), and it is occasionally used with good results in adults (65). The technique is to create a trans-abdominal conduit into the cecum through the appendix or through an artificial channel. The patient is taught to instill an enema fluid, usually containing a laxative, through this conduit daily to empty the colon. In children (63), ~71% become symptom free, 20% improve but remain symptomatic, and 9% are unchanged or worse. Limited experience in adults suggests that this approach is promising, although not always feasible (65,66).

TRANSLATIONAL RESEARCH

Bitar and group (67) developed a technique for harvesting progenitor cells from the anal canal and small intestine, differentiating these into muscle cells and enteric neurons, and combining them to bioengineered intrinsically innervated internal anal sphincter for implantation. They transplanted these neosphincters into a rabbit model of FI and demonstrated that they became vascularized, reinstated continence, and demonstrated reflex activity (recto-anal inhibitory reflex, RAIR). Rattan and Singh (68) also developed a neosphincter from stem cells and demonstrated smooth muscle tone. Thus, regeneration of a functional internal anal sphincter seems achievable. Other advances in understanding the physiological mechanisms for continence include Mittal's observation that the external anal sphincter is a purse-string muscle with attachments to bone rather than a circular muscle(69), and Rattan's characterization of signaling pathways mediating internal anal sphincter tone and phasic contractions (70).

RATING OF EVIDENCE FOR CURRENT TREATMENTS

Table 1 summarizes the strength of the evidence for the efficacy of current therapies and grade recommendations for clinical evidence based on the scoring system of the US Preventive Services Task Force (71). Only three therapies have been assessed

Table 2. Research priorities endorsed by four or more respondents

General priorities	Unmet patient needs	Greatest impact	Highest priority
Pre-conference survey			
Pathophysiology (9)	Special populations (5)	Comparative effectiveness (12)	Comparative effectiveness (12)
Special populations (9)	Biofeedback/ behavior therapy (4)	Access to care (9)	Access to care (5)
Access to care (6)		Pathophysiology (5)	Pathophysiology (4)
Trial design (5)			Develop new treatments (4)
Pads/devices (4)			
End of conference survey			
Definitions/end points (13)	Public awareness (7)	Comparative effectiveness (8)	Treatment algorithms (6)
Regenerative medicine (6)	Biofeedback (4)	Regenerative medicine (5)	Access to care (6)
Access to care (5)		Public awareness (4)	Comparative effectiveness (5)
Multisite clinical trial (4)		Access to care (4)	End point development (5)
		Combined treatments (4)	Classification system (4)
		End point development (4)	

Numbers in parentheses are number of respondents.

by RCTs of sufficient size to justify a recommendation; they are biofeedback, tibial nerve electrical stimulation, and dextranomer injection. SNS is supported by strong level II evidence, but the RCTs reported to date have been limited by selection of patients with structurally intact and innervated external anal sphincters. On the basis of the available evidence, biofeedback merits a strong recommendation for clinical practice, and SNS and dextranomer injections are also recommended for practice. **Table 1** is not intended as a treatment algorithm showing which treatment should be tried first and how decisions about treatment progression should be made. Additional RCTs, comparative effectiveness trials, and tests of treatment combinations are needed to develop a treatment algorithm.

PRIORITIES FOR FUTURE RESEARCH

In addition to assessing gaps in knowledge through systematic reviews of the state of the science, the conference organizers surveyed active investigators about their own priorities for future research. This was done in the following three steps: (1) before the conference, the organizers identified FI investigators by surveying the Medline Database for original research articles on the treatment of FI and emailed a survey to the first and last author of each article published from a US institution; (2) the same survey was distributed to conference attendees on the second day of the conference; and (3) the final session of the conference was an open forum in which conference attendees were invited to identify other research needs. Conference attendees were representative of the field and included gastroenterologists, urogynecologists, colorectal surgeons, nurses, physical therapists, behavioral scientists, geriatricians, public health researchers, and patient advocates. The survey included four open-ended questions: (1) identify important research priorities; (2) list unmet patient needs; (3) indicate which research would have the greatest impact on the field; and (4) identify the highest priority for funding.

Responses to these open-ended questions were grouped into common themes by the first author (WEW) and are listed in **Table 2** in order of frequency of endorsement. Trials comparing the effectiveness, safety, and cost of current therapies were assigned the highest priority for funding and were thought to have the greatest potential impact on the field. A related priority was the development of treatment algorithms. A second major priority was to improve access to care by understanding the barriers that prevent 2/3 of patients with FI from consulting a physician and which explain low rates of physician screening. A related priority was increasing public awareness of FI and reducing the stigma associated with it. Third priority was assigned to research on the pathophysiological mechanisms for FI and translational research on regenerative medicine. Unmet patient needs identified by the conference attendees were the understanding and management of FI in special populations, such as those with neurological disorders, and further research on behavioral treatment strategies, such as biofeedback. Participants also identified the need to involve patient focus groups in the refinement of severity measure and trial end points. They felt that a classification scheme for subtypes of FI should be developed, which is better able to predict responsiveness to specific treatments.

In the open forum at the end of the conference, these same themes were endorsed, and additional unmet patient needs were brought out: (1) among people with FI, ~2/3 have milder, less frequent forms of FI, which may benefit from inexpensive, conservative management techniques. Research to validate such treatments is needed. (2) Cost effectiveness data are needed to improve insurance reimbursement for FI treatment.

Box 4. Key points in design of behavioral and surgical treatment trials

- Patient selection:
  - ✓ Stratify patients on factors likely to influence treatment response (e.g., stool consistency, urge vs. passive FI) before randomization
- Control for difference in interventionist skill and experimenter bias:
  - ✓ Develop a treatment manual and measure adherence to it
  - ✓ Use multiple sites/interventionists
- If masking is not feasible:
  - ✓ Measure expectation of benefit after initial exposure
  - ✓ Mask treatment assignment from outcome assessor
- When comparing established treatments:
  - ✓ Include cost and safety as additional outcome measures
  - ✓ Address reluctance to be randomized by offering to crossover treatment nonresponders to their preferred treatment

RECOMMENDATIONS FOR CLINICAL TRIAL DESIGN

Control groups

A challenge that is unique to the design of RCTs for behavioral and surgical therapies is the impossibility of masking the investigator and patient to whether they receive an investigational treatment. Usual care or symptom monitoring while waiting to receive treatment are not acceptable controls because they create a negative expectancy of improvement for the control group, leading to overestimation of efficacy in the active treatment arm. The preferred solution in behavioral and surgical trials is to compare the investigational treatment with an alternative treatment that generates a similar patient expectation of benefit and to measure expectancy by questionnaire after initial exposure to each treatment. Demonstrating equal expectation of benefit is more important to the integrity of the trial than equal contact time with the therapist (**Box 4**).

Comparative effectiveness trials

Two problems arise when designing trials to compare the effectiveness of two active treatments: (a) if the two treatments are dissimilar (e.g., biofeedback vs. surgery), patients may have strong preferences for one and may be reluctant to be randomized; they may drop out if randomized to their non-preferred treatment. A possible solution to this problem is to design the trial so that patients who fail to benefit from their randomly assigned treatment are offered the opportunity to be crossed over to their preferred treatment. (b) A second problem is that if both treatments are effective, very large sample sizes may be required to detect differences between them. However, the investigator may hypothesize that the two treatments differ on other dimensions such as cost and safety. It is recommended that comparative effectiveness trials be designed with separate *a priori* hypotheses related to efficacy, safety, and cost.

Experimenter bias

Therapist skill and experience influence the effectiveness of behavioral and surgical treatments and should be controlled for by (a) using multiple therapists, (b) drafting a treatment manual before the trial begins, and (c) monitoring adherence to protocol. Outcome testing should be carried out by a blinded assessor.

Patient selection

There are multiple etiologies for FI that can confound efficacy trials: for example, antidiarrheal drugs only help if the patient has diarrhea, and they could worsen constipation. It is recommended to stratify patients at enrollment on the basis of physiological subtypes that may predict response to the treatment under study. It is also recommended to exclude patients with mild or infrequent symptoms to avoid floor effects.

Outcome assessment

Employ validated outcome measures. Define the minimally important difference and/or decide who will be treated as a responder before beginning the trial. There is no consensus on whether to use retrospective questionnaires to assess severity vs. daily diaries vs. quality of life measures, and further research is needed.

Statistical analysis

The primary analysis should be intent-to-treat. Estimate the sample size before the study and include a description of the *a priori* sample size calculation in the manuscript. Comparative effectiveness trials require larger samples to test superiority of one treatment, and noninferiority tests (testing whether the treatments can be considered equally effective) may be more appropriate in some circumstances.

Reporting trial results

Register the trial on ClinicalTrials.gov before enrolling patients. Keep a recruitment log per the Consolidated Standards for Reporting Trials (CONSORT, www.consort-statement.org) guidelines. Describe recruitment strategy, minimum screening process, and randomization method.

SUMMARY

There are several established treatments for FI, which are supported by RCTs. Biofeedback, SNS, and injection of bulking agents have the best evidence and success rates, whether measured as at least a 50% reduction in the frequency of FI or a patient report of "satisfactory relief" ranging from 52 to 76% on an intent-to-treat basis. However, many of the patients classified as successful by these criteria continue to have some FI. Biofeedback outcomes have been highly variable between studies, presumably owing to lack of standardization in the treatment protocols, and the training and experience of the therapist. Several devices (e.g., implantable mesh slings, vaginal balloons to obstruct the anal canal, new artificial sphincters, and anal plugs) are under development and appear promising; however, most device trials are uncontrolled, and RCTs or comparative effectiveness trials will be needed once safety is established.

Conference attendees identified the following as priorities for future research: (1) comparative effectiveness of established treatments, especially surgical vs. behavioral interventions, on the basis of safety and cost as well as efficacy; (2) studies that identify

and overcome patient barriers to medical consultation; (3) investigation of the pathophysiology of FI, especially the potential of regenerative medicine; (4) studies that improve understanding and management of FI in special populations such as those with neurological disorders and nursing home residents; and (5) improvements in biofeedback and other behavioral treatments.

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CONFLICT OF INTEREST

Guarantor of the article: William E. Whitehead, PhD.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ There are effective treatments for fecal incontinence.
- ✓ Differences in research methods make comparisons difficult.
- ✓ No consensus on a common treatment algorithm.

WHAT IS NEW HERE

- ✓ Biofeedback, sacral nerve stimulation, and dextranomer injections are best supported treatments.
- ✓ Multidisciplinary conference identified priorities for future research.
- ✓ Consensus recommendations for study design provided.

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