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Endpoints for Therapeutic Interventions in Fecal Incontinence: Small Step or Game Changer

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Abstract

Fecal incontinence (FI) is common and its pathophysiology and treatments continue to evolve. However, a standard measure(s) for assessing its clinical outcome has been elusive. Consequently, over 100 measures and scoring systems, each with intrinsic biases have been reported. These include adequate relief or global satisfaction, 50% reduction in episodes or days without FI, quality of life (QOL), FI severity scales and composite indices. Earlier scales relied on the frequency and type of solid, liquid or flatus incontinence and effects on life style whereas newer scales have incorporated urgency, use of pads, antidiarrheals and amount of leakage, using prospective daily stool diaries or retrospective weekly or single point assessments. Such a plethora of measures have negatively impacted the assessment and outcome of clinical trials, and have made comparisons difficult. So, how does one sort out the grain from the chaff? In a provocative, post-hoc analysis published in this issue, the minimal clinically important difference, i.e. the smallest change detected by an instrument that is associated with a clinically meaningful change was used to assess FI endpoint. Based on this a 50% reduction in FI episodes is recommended as a clinically meaningful outcome measure when assessed by stool diary, and it correlates with symptoms and severity. However, this requires further validation in multi-center, longer duration and therapeutically effective clinical trial(s). Simultaneous assessment of coping strategies, QOL and psychosocial domains can provide further insights regarding the overall impact of treatments. This mini-review discusses the advances and controversies in defining meaningful FI endpoints.

Graphical Abstract

Keywords

Fecal Incontinence; Outcomes; Endpoints; Treatments; Stool Diary

INTRODUCTION

Fecal incontinence (FI) is defined as the recurrent uncontrolled passage of fecal material for at least three months, when not related to an acute diarrheal illness (1). The prevalence of FI varies between 7–15% in community-dwelling women, and is at least 2–3 fold higher in nursing home residents (1,2). It profoundly affects quality of life, and causes significant social and psychological distress (1,2).

Pathophysiological assessments

Because normal continence is maintained by several mechanisms, a failure of multiple factors can contribute to FI (1,3–8). Diarrhea, rectal urgency, obstetric injury, surgical injury, neurological injury, cholecystectomy, smoking, obesity, stress urinary incontinence, advanced age, diabetes and decreased physical activity among others are all independent risk factors (1–4). FI is therefore a heterogeneous disorder with a majority of patients exhibiting more than one pathophysiological deficit including anal sphincter weakness, puborectalis weakness, rectal hyposensitivity or hypersensitivity, neurological injury, impaired rectal compliance, dyssynergia, excessive stool retention and overflow (1,3,6). Consequently, both from a clinical diagnosis and treatment perspective, the assessment of FI has been challenging.

A detailed history, digital rectal examination and characterization of stool habit (Bristol Stool scale) is useful (6). Urge versus passive FI or fecal seepage can provide clues regarding underlying pathophysiology (4). Patients with urge incontinence have a sensation for stooling before leakage but are unable to reach the toilet on time. Conversely, patients with passive incontinence have little or no awareness of stooling before the incontinent episode (4). Patients with urge incontinence often have reduced squeeze pressures and/or squeeze duration, reduced rectal capacity and rectal hypersensitivity, whereas patients with passive incontinence often have lower resting pressures and neuropathy (3–6). Patients with

fecal seepage have rectal hyposensitivity and dyssynergic defecation causing incomplete evacuation and seepage of retained stool. (7) Incontinence for solid stool suggests more severe sphincter weakness than liquid stool alone (8).

How efficacious are treatments for FI?

Because of multitude etiological, pathophysiological and risk factors, it is not surprising that the assessment of FI has been daunting. Several reviews that have examined evidence-based treatment options have concluded that there was limited evidence to guide clinicians for selecting FI therapies and strength of recommendation for most studies was moderate or weak (9–11). A recent in-depth study of all randomized controlled trials for FI by the Agency for Healthcare Research and Quality (AHRQ) analysis also arrived at a similar independent conclusion that the strength of past studies was weak or moderate, there was moderate or high risk of bias, the measurement tools were quite diverse, and firm recommendations could not be made for any of the treatments (12).

It is possible that the therapies are ineffective or only partially effective in correcting the underlying mechanism(s) or the instruments and measures that have been used to assess treatment response have not been vetted properly or they are not robust enough to demonstrate improvement or both. This mini-review discusses the advances and controversies in defining patient-reported, meaningful FI endpoints and composite scales, and critically examines their utility in the context of recent randomized controlled trials, and a publication validating FI endpoints by Noetting et al (13) in this issue..

EVALUATION OF FI USING STOOL DIARIES

How does one assess FI?

A detailed history based on the patient's recall of bowel symptoms can help to characterize the problem for a clinician, and provide some pointers for defining its clinical subtype and severity (1,6,13), but these are heavily influenced by recent events or those that have had a profound effect on the patient's life. In contrast, prospectively maintained 1–2 week stool diaries that record stool frequency, stool consistency (Bristol stool scale 1–7), urgency, severity and volume of stool leakage, use of pads or medications may provide more accurate information (1,6,13). In a prospective study, Bharucha et al (14) assessed daily stool diaries and showed that it provides reliable insights regarding bowel patterns and FI, and avoided recall bias. Arguably, filling out daily paper stool diaries can be cumbersome, especially for the assessment of long term treatment(s) (15). In one long-term trial of sacral nerve stimulation (SNS), intermittent 2-week stool diaries were used along with questionnaires to assess improvements, and proved effective (16). But with the advent and increasing use of smart phones, and user friendly apps on mobile devices, it is possible to design electronic diaries that can prompt its owner to record their bowel habit prospectively, on a daily basis, and thereby also facilitate accurate data analysis.

Frequency of stool diary assessments

Should bowel symptoms be assessed daily or can they be assessed using weekly diaries? Generally one would assume that daily stool diaries that are less subject to recall bias are

more accurate. Interestingly, Noelting et al (17) showed that FI symptoms and severity assessed by weekly diaries correlated well with daily diaries ($r=0.9$, $p<0.001$). This finding was however based on a short four-week clinical trial (18) where such an agreement is possible. But whether a weekly symptom diary is as accurate as a daily stool diary will need to be independently confirmed through a larger, multicenter and longer duration (3–6 month) clinical trial. This is because retrospective self-reports, just as weekly diaries or global rating of change, are subject to recall bias, and have a tendency to reflect the patients current state of health, much more than a change from their baseline, and therefore possibly inaccurate.

FECAL INCONTINENCE SEVERITY, COMPOSITE INDICES AND PSYCHOMETRIC ASSESSMENT

Because episodes of stool leakage do not provide an accurate measure of FI as a sole measure, several composite scales have been proposed for the evaluation for FI, although many have not undergone psychometric testing. A systematic review by AHRQ revealed that 105 single or composite measures have been used for assessing improvements in 62 randomized controlled trials (RCTs) of FI (12). Additionally 6 QOLeg; short form 36 (SF-36) or Fecal Incontinence Quality of Life (FIQL) measures, 4 health status measures (Physical/social handicap or short form 12 (SF-12), and 12 miscellaneous measures such as antidiarrheal medication use etc. have been used (12). Therefore, not surprisingly, they could not perform a meta-analysis of FI treatments, and concluded that there was limited evidence to support any treatment. They felt it was difficult to compare the effectiveness of surgical versus nonsurgical therapies, and most current interventions that meet minimally important differences in the short term only show modest improvements in FI outcome. This disparity was primarily due to a lack of universal standard outcome measure and lack of compliance with study reporting standards (12).

Over the last two decades, assessment of severity of FI has largely comprised of 3 distinct measures: a) loss of fecal material, b) use of coping strategies (eg. wearing a pad), c) impact or alterations on life style. Browning and Parks (19) first proposed a simple scoring system based on solid or liquid stool or flatus incontinence, and it was weighted in favor of solid stool as opposed to liquid stool FI. Subsequently, Miller et al (20) proposed a scale based on both the degree and frequency of FI, and this was further modified to increase the sensitivity of stool frequency scale to a score of 6 points (21).

Subsequently, Jorge and Wexner (22) proposed the first incontinence scoring system that incorporated the use of pads and lifestyle changes along with stool consistency and frequency, each scored on a scale of 0–4 with a total maximum score of 20. This scale has remained popular, particularly in the surgical literature, with reports of 21 RCTs using this scale, possibly because of its simplicity (12). However this scale is anchor-based and derived from a patient perspective and not distribution based i.e., was not based on exceeding a minimum clinically important improvement threshold derived from either standard duration or standard error of the mean. Also it is not weighted, does not assess urgency, and the use of pads was weighted equally with stool loss and may not be an accurate measure of incontinence but more of personal hygiene (23). Because of these inherent weaknesses and

high risk of bias, several trials that have used this score as the primary outcome measure have often reported positive results in favor of the treatment but have been seldom replicated (12).

A refinement of this score was proposed that included the need to take antidiarrheal medication, (no = 0 or yes = 2), and the ability to defer or postpone defecation for 15 minutes (a measure of stool urgency), scored on a scale of (0 = no to 4= yes) with a total score of 24 (23). Psychometric assessments were performed including independent physician assessment of symptoms, patient assessment using prospective stool diaries for 28 days, validation against healthy controls, test-retest reliability, and therapeutic responsiveness before and six weeks after surgery and comparative analysis with other scores (23). These assessments showed that this correlated well with clinical assessments, was reproducible and sensitive enough to reflect treatment response, and that it was more reliable and sensitive than their comparators. Subsequently, it has been used in 10 RCTs (12).

Rockwood et al (24) proposed the Fecal Incontinence Severity Index (FISI) as a measure of gas, mucus, liquid and solid stool leakage. This index comprised of 5 frequencies ranging from 1–3 times a month to twice per day, and used both physician and patient input (24). Because all types of FI or coping mechanisms or frequencies of FI are not equal, an externally weighted measure derived from patient rating and physician rating was applied to the frequency to arrive at a patient-rated severity from 0–61 and physician-rated severity from 0–59 (24). Thus, this was both an anchor and distribution based measurement. In 118 patients they showed that patients and physicians had similar weightage for severity and it correlated with QOL scales. This measure has been used in 5 trials (12).

Bharucha et al (25) have validated the FICA (Fecal Incontinence and Constipation Assessment) scale now termed the FISS (Fecal Incontinence Severity Scale) in women with FI. This incorporated rectal urgency, which is often unpredictable, and causes much distress, similar to Vaizey (23), , as well as type, frequency and amount of FI. From this a QOL-weighted symptom severity score was derived. Patients with urge FI and rectal hypersensitivity had more frequent stools, used more pads, and reported more lifestyle restrictions when compared to patients with normal rectal sensation (25). Also the FICA severity score correlated well with QOL severity (27).

The bowel version of the International Consultation of Incontinence questionnaire (ICIQ-B) is the most recently developed patient-reported outcome measure (26). It includes 17 items under 3 domains; bowel patterns (5 items), bowel control (7 items), and quality of life (5 items), most rated on 5point Likert scale (26). In a study of 65 patients this questionnaire showed good internal consistency, test-retest reliability and QOL impact and reasonable responsiveness to usual care of non-surgical treatments (28). However, this needs further validation in RCTs.

Rapid assessment of fecal incontinence severity (RAFIS) is the latest scale proposed by a Spanish colorectal surgery group as a rapid tool for the assessment of clinical severity, and its impact on physical and emotional well-being (29). It comprises of 2 scales; the state of

the subject represented by various faces and measured on a VAS (0= you feel very good to 10= you feel very bad) and the frequency of leakage measured by 6 ordinal scales varying from several leaks daily (score 10) to no leaks (score 0). It has been validated in 53 FI patients and 208 healthy subjects (29). However construct validity, test-retest reliability and therapeutic responsiveness has not been shown for this anchor-based measure, and it does not assess several other quantifiable measures of FI proposed in other scales.

Quality of Life Assessment

Because FI is a multifactorial illness that not only affects the physical state but also QOL and psychosocial traits, it has been argued that an assessment of improvement in FI must take into account these other domains in order to best reflect the overall improvement. This argument has formed the basis for inclusion of some of these parameters in FI scales. Rockwood et al developed the FIQL scale that was both anchor and distribution-based and validated its use in clinical trials (12,25,30). This scale has been embraced by many investigators and has been used in 21 RCTs of FI (12).

Interestingly, in a large study of 502 consecutive FI patients that completed FIS, FIQL and SF-36, there was moderate correlation for FIS and FIQL subscales, but weak correlations for social functioning and mental health, particularly depression, attesting that these domains may be independent of each other (31,32). Some have suggested that depression has a stronger influence than anxiety on QOL in FI, although like others they did not observe a significant correlation of FIS with bowel satisfaction or QOL in a short-term 4-week intervention (17). Some measures of QOL domains are also incorporated in several composite indices (25,26). These findings suggest that the physical, social and psychological domains are independently affected in FI, and therefore should be assessed separately, in order to evaluate the true impact of any intervention (Figure 1), and that short term studies that may improve FI may not affect QOL and psychosocial domains.

DEFINING AND VALIDATING A FI ENDPOINT

Although innumerable measures, scales and composite indices have been used, there is no acceptable gold standard or outcome measure. A selected list of recent RCTs (33–43) spanning medical, biofeedback, injectable and surgical interventions are summarized in Table 1. This highlights the disparities in subject selection, trial design, outcome measures and risk of bias. Consequently, the assessment of individual treatment(s) or comparative effectiveness of treatments has been problematic (9–11,12). In recent years, success in therapeutic trials has been defined as a 50% reduction in the number of episodes of FI or days per week of FI (28,38,43,44). Several recent trials have used this benchmark (Table 1) which is favored by the FDA. Using this benchmark, Dextranomer injection into the anal canal was shown to be superior to placebo injection (38), whereas oral clonidine was not beneficial when compared to placebo in FI (28) and a sham controlled multicenter trial showed that Percutaneous Tibial Nerve Stimulation (PTNS) was not effective (43) (Table 1). However, it has been argued that a 50% reduction in the frequency of FI (e.g., from 3 episodes per week to 1.5 per week) may not be clinically meaningful from a patient's

perspective, as the degree of improvement may not allay fears of an imminent accidental leakage in a given patient (44).

So how does one determine whether a statistically significant change in FI episodes is also clinically meaningful and significant? This is best accomplished by using the minimum clinically important difference (MCID), which is the smallest change detected by an instrument that is associated with a clinically meaningful change (45). When determining MCID, it is recommended that a patient's perspective be given most weight, although a physician's perspective should be considered (46). MCID can be evaluated with anchor and distribution-based approaches. Anchor based approaches assess responsiveness in relation to an independent measure (eg another rating) (45). Distribution-based approaches define the MCID as any change that exceeds 0.5 SD for that parameter at baseline. This was estimated by using 3 anchor-based approaches such as the patient's perspective (global rating of change) and 2 clinical measures and 1 SEM in urinary incontinence (47). Using this approach they were able to define and validate the minimal scores for urinary distress, severity and QOL. Similarly, one study used anchor-based approaches to identify the MCID for the FISFI and other scales in FI (48).

Applying the MCID perspective, but only using the distribution-based estimates, Noelting et al (17) observed significant associations between changes in FI frequency and global endpoints such as fecal incontinence severity score (FISS), and global satisfaction with improvement in FI using a Visual Analog Scale (VAS). When the frequency of FI episodes decreased by 50–74%, the FISS result exceeded the MCID ($0.5 * SD$ threshold) in 75% of patients, and when it decreased by 75% it exceeded in 83% of patients. Even using a more stringent MCID of 1.0 SEM, 75% and 50% of patients reported clinically important improvement with >75% reduction, and 50–74% reduction in FI episodes. Thus, although a >75% reduction is superior, their study clearly demonstrated that for clinical purposes a 50% or greater reduction in FI episodes over baseline is clinically meaningful. However, unlike some other studies they did not observe corresponding changes in QOL, possibly because of the short duration of study, ineffective treatment, a type II error or because the QOL was more strongly influenced by perceived health than by FI severity. Similar observations have been reported in other FI treatment studies, for example with dextranomer there was no change in QOL (38) and in a longer term Sacral Nerve Stimulation (SNS) study only 5–15% of variance in FIQOL was explained by changes in FI severity (49).

DISCUSSION AND CONCLUSION

Thus, although innumerable outcome measures have been proposed and tested, a lack of well-validated end point has hampered research and assessments of treatment response in patients with FI. More recent interventional trials have embraced the use of 50% reduction in FI episodes as a useful outcome measure for evaluating efficacy (28,38,43), but without a sound rationale. However, Noelting et al (17) in this issue, provide for the first time a credible scientific basis and validation for using this parameter as a minimal, clinically meaningful and useful primary outcome measure. Although this finding merits independent validation in multi-center, longer duration and therapeutically effective clinical trial(s), moving forward a 50% reduction in FI episodes is recommended as the standard

measurement for defining clinical outcome in FI (Figure 1). However, it should not be applied in isolation, but in prospectively designed randomized controlled trials (RCTs) so as to avoid any bias (1,28,44). FI also involves multiple domains including coping strategies, affects on QOL as well as psychosocial domains that cannot be assessed by evaluating FI episodes alone (Figure 1). Furthermore, there appears to be a disconnect between improvements in bowel symptoms and changes in QOL and psychosocial domains (12,32), (Table 1). Hence, when planning clinical studies, all 3 broad domains should be assessed using validated scales (Figure 1), but it is important to define apriori the primary and secondary outcome measures. Together, they will provide a clear assessment of the overall impact of an intervention. Only by applying such rigorous and validated measures in well-designed RCTs can one hope to change the therapeutic landscape of FI.

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Key Points

- Fecal incontinence is a heterogeneous, multifactorial disorder. Consequently, a single standard measure for assessing its clinical outcome has been challenging.
- Innumerable scoring systems and measurements that include assessments of bowel symptoms, incontinence episodes, effects on quality of life and coping strategies, and psychosocial domains have been proposed, but have not been validated.
- A reduction in fecal incontinence episodes/week by 50%, when assessed by prospective stool diaries, appears to be a valid and clinically meaningful outcome measure, and it correlates well with bowel symptoms and its severity.
- Additionally, quality of life and psychosocial domains should be assessed in order to optimally examine the impact of an intervention when treating fecal incontinence.

Figure 1.

Schematic proposal for the assessment of fecal incontinence in randomized clinical trials. Bowel symptoms, Quality of life and Psychosocial domains should be assessed separately and used to derive the primary and secondary outcome measures.

Table 1

Selected summary of recent (<10 year) randomized controlled trials for the treatment of fecal incontinence, illustrating the plethora of outcome measures, the variability in treatment efficacy, and the risk of bias with study design and interpretation of results

Treatment intervention	Author, Year	Study Purpose	n= number of subjects; Female(F); FI Etiology; Treatment(T) and Follow-up duration(FU)	Study Groups (n)	Outcome measures (bold=primary outcome)	Treatment efficacy	Adverse effects	Risk of Bias
Dietary fiber	Bliss ³³ , 2014	Compare fiber supplements	n=206 F=74% NR T= 38 days FU= 38 days	T1=carboxymethyl-cellulose (CMC) (53) T2=gum arabic (50) T3=psyllium (54) C= placebo (49)	FI frequency , amount, consistency, severity; FIQL	FI frequency significantly decreased after psyllium supplementation versus placebo, in both intent-to-treat and per- protocol mixed model analyses. FIQL scores did not differ among groups	Overall: NR Methylcellulose: 11% Gum Arabic: None Psyllium: 11% Placebo: None GI symptoms, bloating, gas and allergic reaction most common.	Low
Clonidine	Bharucha ¹⁸ , 2014	Effectiveness of clonidine vs. placebo in women with FI	n=44 F=100% Mixed T= 4 weeks FU=4 weeks	T=Clonidine oral 0.2mg/d (22) C=Placebo (22)	FICA , >50% reduction of FI episodes from baseline, days of FI, FIQL, FISI, HAD, satisfaction, rectal urgency, loperamide use	Overall, clonidine did not affect bowel symptoms, fecal continence, or anorectal functions, compared with placebo, in women with urge-predominant FI.	Overall: No serious AEs. Clonidine: 86% nonserious AEs Placebo: 32% nonserious AEs Dry mouth, fatigue, light-headedness and drowsiness most common.	Low
Biofeedback	Damon ³⁴ , 2014	Does PEMT-BF plus standard care improve FI outcomes over standard care only?	n=92-142 (varied per analysis) F=77% Mixed T=4 months FU=4 months	T= PFMT-BF (20 sessions) plus standard care (77) C=standard care of laxative, oral bulking agent, loperamide (80)	Treatment effectiveness (-5 to 5), CCFFIS, FIQL, KESS, SF-12, symptom change	In the biofeedback group, daily stool frequency, leakage, and fecal urgency significantly decreased, and daily non-urgent perception of stool increased.	No AEs	High
Biofeedback	Heymen ³⁵ , 2009	Does BF improve FI compared to pelvic floor exercise (PFE)	n=108 F= 86% Mixed T= 12 weeks	6 sessions/12 weeks T= Biofeedback (45)	Adequate relief of symptoms , FISI (at 12wk); FIQL, FI count, STAI-1, STAI-2, BDI	BF group had greater (P<0.001) improvement in adequate relief of bowel symptoms	No AEs occurred	Low

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Low versus Medium frequency electrical stimulation (ES) + EMG Biofeedback (BF)	Schwandner ³⁶ , 2011	Does medium frequency ES +BF improve FI compared to low frequency ES +BF?	n=80 (ITT) F=81% Mixed T=6 months FU=3 months, 6 months	T= ES (medium freq) with BF (39) C= ES(low freq.) with BF (41) C= PFE "alone" (63)	CCFIS, adapted Vaizey (0-24), FIQL, ICIO-SF, % complete responders	(76%) vs PFE exercises group (41%) and had greater reduction in FISI compare to PFE alone.	Overall: NR T: None C: 50%; pain during ES most common	Moderate
Dextranomer Injection	Dehli ³⁷ , 2013	Are injections with dextranomer superior to pelvic floor exercises (PFE) with biofeedback (plus electrical stimulation (ES) if needed for FI	n=119 (6 mo) F= 93% Mixed T= 6 months FU=6 months(RCT to 6 months; observed successes to 2 years)	T= Dextranomer in hyaluronic acid (4 x 1ml injections into anal submucosa); repeat 1x if needed (64) C: PFE + BF + ES if needed x 6 sessions/6 months (62)	Vaizey ("St. Mark's" 0-24), FIQL, EQ-5D	Improvement in Vaizey score was comparable between biofeedback and dextranomer injection groups	Overall: NR T: 25%; leakage of injected agent, prolonged defecation most common C: 8%; pain using anal probe most common.	Low
Dextranomer Injection	Graf ³⁸ , 2011	Does injection of dextranomer into the anal canal submucosa improve FI over sham injections?	n=197 (6 mo); 125 (1 yr treated only) F= 89% Mixed T= Injections (1 d); repeat in 1 month if CCFIS >10 FU:=3 months, 6 months; 1 year for treated group	T=Total of 4-8 ml dextranomer injections in four quadrants of anal submucosa (136) C=Sham injections (no substance injected) (70)	>50% reduction of FI episodes/week from baseline CCFIS, FIQL, number of FI-free days, decrease in FI episodes	FI countsL/wk decreased more than 50% from baseline in dextranomer injection group VS 21% in sham treatment	Overall: NR Serious AEs: T= rectal abscess (1%), prostatic abscess (1%) C=None Nonserious AEs: T= proctalgia (14%), rectal hemorrhage (7%), diarrhea (5%), constipation (2%), injection site bleeding (5%), rectal discharge (4%), anal pruritus (2%), proctitis (3%), painful defecation (2%),	Low

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							fever (8%), other (16%) C= proctalgia (3%), rectal hemorrhage (1%), diarrhea (4%), injection site bleeding (17%), others (7%)	
Durasphere Injection	Tjandra ³⁹ , 2009	Compare perianal injection of bulking agents Durasphere® (off- label) vs. PTQ™ (not FDA approved) in FI	n=40 overall F=90% Mixed T= 1 d FU:=2 weeks, 6 months, 1 year	T1= Durasphere®: perianal injection (20) T2=PTQ™ (not-FDA approved) (20)	CCFIS , FIQL, SF- 12	PTQ group significant improve CCFIS, FIQL and SF-12 compared with Durasphere group.	Overall: NR T1:=Serious AEs: rectal pain (5%), erosion through rectal mucosa (10%), hypersensitivity reaction (required hospitalization & IV steroids, 5%). Nonserious AEs= bruising (20%). T2: NR	Low
Sacral nerve stimulation (SNS)	Duelund- Jakobsen ⁴⁰ , 2013	Compare higher frequency of SNS vs standard frequency SNS in the patient who had sustain loss efficacy of SNS	n=15 F: NR NR T: 4 week each setting FU: 3 months,	T1: 14Hz/210µs T2: 6.9Hz/210µs T3: 31Hz/210µs T4: 14Hz/330µs T5: 14Hz/90µs Crossover randomized study	FIQL , CCCS, SMFIS, VAS	High-frequency stimulation (31 Hz/210 µs) was preferred by more than half of the patients, and improved treatment outcome was sustained at 3 months	Overall= NR	Moderate
Sacral Nerve Stimulation	Tjandra ⁴¹ , 2008	Compare SNS vs supportive therapy including PFE.,bulking agent, diet manipulation	n=40 overall F= 92% Mixed T= 1 day FU=12months	T=SNS with implant stimulator C=PFE,bulking agent, diet manipulation	Wexner' score , FIQL , SF-12 , FI count	In SNS, there was a significant improvement in FIQL, Wexner's score, and FI count at 3 and 12 months.	T=Surgical implant complication such as infection should be considered. C= NR	Moderate
Percutaneous Tibial Nerve Stimulation	Thin ⁴² , 2015	Compare PTNS with SNS	n=31 F= 98% Mixed	T: PTNS 15 sessions: 12 in 3	FI episodes , CCFIS , SF-36, EQ-5D; qualitative interview	FI episodes, CCFIS, SF-36, EQ-5D were	No serious AEs occurred	Moderate

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(PTNS) vs. Sacral Nerve Stimulation (SNS)			T= 5 months (PTNS) FU=3 months, 6 months	mo, plus 3 over 2 mo. (16) C: SNS (15)		comparable between two groups	Nonserious; T= transient paresthesias (6%) or pain (6%). C= 20%; leg pain or site pain (resolved)	
Percutaneous Tibial Nerve Stimulation (PTNS)	Knowles ¹² , 2015	Compare PTNS with Sham electrical stimulation	n=227; F=90%, Mixed, T= 12 weeks (12 sessions), FU: 14 weeks	T= PTNS 30 mins once/week for 12 sessions, C=sham stimulation	>50% reduction of FI episodes/week from baseline Vaizey, FI(QL, SF-36, EQ-5D-3L	PTNS given for 12 weeks did not confer significant clinical benefit over sham electrical stimulation	No serious AEs occurred Pain at needle site, n=7 Bleeding, n=5 Paresthesias, n=2	Low

AE=Adverse Effects; BDI=Beck Depression Inventory; BM=bowel movement; CCFIS=Cleveland Clinic Fecal Incontinence Score also known as Wexner's score (22); C=Comparator/control; dx=diagnosis; diary; EQ-5D-3L=EuroQoL Questionnaire-5 Dimensions and 3 level instruments; F=Female; FI=Fecal incontinence; FICA=Fecal Incontinence and Continence Assessment; FIQL=Fecal Incontinence Quality of Life scale; FISI=Fecal Incontinence Severity Index; FU=Follow up; FDA=Food and Drug Administration; freq=frequency;; HAD: Hospital Anxiety and Depression Scale; ITT=Intention-to-treat analysis; M=Male; NR=Not Reported; NSD=No Significant Difference; PP=Per protocol analysis; PTNS=Percutaneous tibial nerve stimulation; PTQTM=injectable bulking agent not FDA approved for use in the US; QoL=Quality of Life; reps: repetitions; SAE=Serious Adverse Event; SF-12=Short-Form-12 health survey; SF-36=Medical Outcomes Study Short-Form 36-item Health Survey; STAI=Spielberger State Trait Anxiety Inventory ; surg=surgery; T1=Treatment group 1 T2=Treatment group 2 T3=Treatment group 3; Vaizey=Vaizey Fecal Incontinence Score (23); VAS=Visual Analogue Scale;