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**Neuromodulation for fecal incontinence: An effective surgical intervention**

Chiarioni G *et al.* Neuromodulation for fecal incontinence

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**Abstract**

Fecal incontinence is a disabling symptom with medical and social implication including fear, embarrassment, isolation and even depression. Most patients live secluded and have to plan their life around the symptom with secondary impairment of their quality of life. Conservative management and biofeedback therapy are reported to benefit a fair percentage of those affected. However, a surgical approach has to be considered in the non-responder population. Recently, sacral nerve electrostimulation lately named neuromodulation has been reported to benefit fecally incontinent patients in randomized controlled trials more than placebo stimulation and some conservative management by unknown mechanism. Neuromodulation is a minimally invasive procedure with a low rate of adverse events and apparently favorable cost-efficacy profile. This review is meant to expand the knowledge about this effective intervention among the non-surgically skilled community who deals with this very disabled group of patients.

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**Key words:** Fecal incontinence; Neuromodulation; Sacral nerve stimulation; Biofeedback; Anal sphincter

**Core tip:** This technical review aims to report the summary of evidence for neuromodulation treatment of fecal incontinence providing additional hints to improve interpretation of the outcome: (1) Neuromodulation is effective treatment for some patients with fecal incontinence of different etiologies; when analyzed by intent to treat analysis, the median responder rate is 59%; (2) The mechanism/s by which neuromodulation improves anal continence is unknown; (3) Neuromodulation is a minimally invasive procedure. The most common serious adverse event is infection at the site of implant which occurs in approximately 3% and requires device explant in approximately 3% of all patients receiving permanent implants; (4) Cost of treatment is high relative to conservative treatment and biofeedback but studies in three different countries suggest it is cost-effective when offset by gains in quality adjusted years; and (5) Randomized controlled trials comparing neuromodulation with biofeedback therapy in fecal incontinence would be advisable to tailor patients’ management

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**INTRODUCTION**

Fecal incontinence (FI) defined as the accidental loss of solid or liquid stools is a common disabling condition often under-reported on medical consultation for fear and embarrassment. In a recent study considering more than 1500 primary care patients, FI was self-reported by 36.2% of subjects, but only 2.7% of them had a medical diagnosis of fecal incontinence[1]. FI has significant impact on quality of life and health expenses and may facilitate the placement of older patients in nursing home facilities[2]. Therefore, increased medical screening of FI is needed since both conservative and interventional treatments are available. Biofeedback therapy to increase rectal awareness to stool and ameliorate anal sphincter response have been reported to improve continence in about two third of patients in both open and randomized controlled trials [3,4]. However, patients with a severe impairment of rectal sensation and/or previous anal trauma do poorly with biofeedback and alternative options are desirable in selected patients [5]. In the past a number of surgical procedures has been proposed to treat FI. Major drawbacks were the small samples commonly studied and the potential worsening of incontinence occasionally observed [6]. Sacral Nerve Electrostimulation, later also named Neuromodulation (NRM), was first applied in 1995 by Matzel *et al*[7] with encouraging results in a small group of fecally incontinent patients without evidence of anal sphincter defects. The technique was appealing for limited side effects and for being poorly invasive. Since then, the effectiveness of NRM in improving FI has been proven in a number of studies while its mechanism/s of action remain ill defined[8]. However, Physicians involved in the treatment of disordered anal continence should consider NRM among potential treatment options and this review is meant to be a primer for the non-surgical community.

***Search methods***

Search terms were fecal incontinence OR anal incontinence and sacral nerve stimulation OR neuromodulation. These searches were limited to human subjects, adult subjects, and studies published in full in English language spanning the interval between January 1995 and December 2012. Case reports, preliminary studies, and small sample series investigating less than 15 patients were not considered. Databases searched were PubMed, Web of Science, Cochrane Reviews, and EMBASE. The bibliographies of identified studies were also searched for additional references. To address NRM effectiveness, privilege was given to randomized controlled trials and adequately powered prospective trials.

**TECHNIQUE, SAFETY AND MECHANISM/S OF ACTION OF NRM**

***Technique***

NRM is a two stages minimally invasive surgical intervention consisting of: (1) a testing evaluation interval, (2) a second stage with permanent stimulator implant, provided the testing interval results clinically successful. The first stage, also termed percutaneous nerve evaluation (PNE), is of most relevance to determine the feasibility of electrode implantation into the sacral foramina and to evidence clinical benefits worth pursuing permanent NRM [9]. Two technical options are available for PNE: a temporary, percutaneously placed, unipolar stimulation lead to be later removed or the surgical placement of a quadripolar lead next to a target nerve [9]. Both type of leads are then connected to an external pulse generator to be substituted by a permanent pulse generator implanted subcutaneously in case of positive outcome. The permanent implant sized a quarter dollar-two euro coin is commonly placed in the gluteal area and can be managed by a small handheld device [9]. A small retrospective study evaluated outcome and complications of the two PNE techniques [10]. No difference in outcome was shown, but the infection rate was slightly higher in patients undergoing surgical placement.

***Safety***

The commonest adverse events are implant site pain and paresthesia, which is seen in up to 28% in some large series with careful reporting about safety [11,12]. Pain is usually managed conservatively and explant of the device is very rarely needed. However, a recent meta-analysis concluded that implant site pain may show figures as little as 6% [8]. The most serious complication is infection at the implant site, which is seen in up to 10.8% in the largest series of over 100 patients [11,12]. The control of site infection may require device explant in approximately half of those affected [12]. The meta-analysis by Tan *et al*[8] supports diverse evidence indicating that the typical infection rate is 3% with the proportion requiring the device to be removed for refractory infection being about 3%. Additional side effects reported in less than 8% of patients are urinary incontinence, diarrhea, and extremity pain always spontaneously resolving or effectively managed by medications [8]. In older series, broken or displaced electrodes occurred in about 4% [8], and sometimes did require device explant. However, this problem is becoming less frequent since the electrodes were redesigned. Battery replacement is usually required after a median of 7 years [13].

***Mechanism/s of action***

In 1999 Vaizey *et al*[14] first reported the effect of NRM on anorectal physiology measured by 24 h solid state catheter manometry in a small group of 10 patients with fecal incontinence. Resting anal pressure did not change significantly while some evidence of modification of rectal sensitivity and tone were provided. The Authors speculated that NRM worked via complex neuromodulation of sacral reflexes to regulate rectal sensitivity and anorectal motility [14]. Since then, a number of studies focused on anorectal physiology modifications associated with NRM in FI with conflicting results. In his meta-analysis, Tan *et al*[8] concluded that NRM is associated with an improvement in anal canal pressures both at rest and with voluntary squeeze, plus a decrease in the maximum tolerable rectal volume. However, subsequent studies have shown inconsistent results, with randomized controlled trials (RCTs) and long term studies failing to show a relevant influence of NRM on anal pressures [15,16]. When there are significant improvements in anal canal pressures the effect size is small and the final resting and squeeze pressures appear to be below the normal range for healthy controls [8]. This is not commensurate with the large clinical effects seen for FI and suggests that the mechanism by which NRM improves continence is not primarily an improvement in anal canal pressures. The issue was deeply addressed in a recent review by Gourcerol *et al*[17] specifically focused on defining potential mechanism/s of action of NRM. The Authors speculated on three potential mechanisms of action: (1) a somato-visceral reflex, (2) a modulation of the perception of afferent information, and (3) an increase in external anal sphincter activity [17]. However, no definitive evidence could be found to support any of these and a multifactorial component was further speculated to justify the efficacy of NRM. The Authors concluded that NRM is effective almost certainly *via* modulation of spinal and/or supra-spinal afferent inputs, but many gaps remain in the understanding of mechanism/s of action of NRM [17].

**EFFECTIVENESS**

After the early Matzel’s report, a number of trials were developed to evaluate the efficacy of NRM in FI [8]. A major drawback to assessing this Literature is the huge variance in inclusion criteria, outcome criteria, and follow-up intervals [8]. Additional limitations were small sample size (often less than 20 patients studied) and lack of adequate control groups [8]. However, the majority of uncontrolled trials reported a favorable outcome in more than two third of patients with limited side-effects 8. Researchers were unable to identify any clinical and/or functional variable that could predict outcome [8]. In earlier reports, patients were selected on findings of either no or marginal evidence of anal sphincter defects. However, this limitation was later dropped for the unclear definition of the treatment’s mechanism of action [8]. In 2005, Leroi *et al*[18] reported on the first randomized, controlled, double blind, multicenter study testing the efficacy of NRM in FI and/or severe urgency of any etiology. Patients with an ultrasound diagnosis of sphincter defect were included, provided the defect was not considered to be the main determinant of incontinence [18]. After implantation, 27 out of 34 FI patients were randomized in a double blind cross-over design on NRM active treatment (Electrostimulator ON) *vs* placebo (Electrostimulator OFF) for a 1 mo period with the device “*in situ*”. A final interval of three months was also included in the evaluation with patients still blinded potentially choosing either the ON or the OFF modality [18]. Twenty four patients only completed the trial making the sample underpowered. However, patients reported a significant improvement in both symptoms and quality of life (QOL) scores, and anal physiology when in active treatment compared to placebo providing evidence that a placebo effect was not a main determinant on NRM outcome [18]. However up to recently, NRM was not compared to conservative management (diet, life style, constipating drugs, biofeedback) which is cheaper, commonly available and associated with benefits in a fair percentage of FI patients up to recently [3]. To address the issue Tjandra *et al*[15] randomized 120 FI patients to either supervised optimal medical therapy or NRM. Conservative treatment included bulking agents, pelvic floor exercises, lifestyle and dietary manipulations, but it did not include biofeedback [15]. NRM was significantly more effective on improving frequency of incontinence with 25 patients regaining perfect continence [15]. Cleveland Clinic Continence Score and QOL score were both significantly improved as well [15]. In a recent prospective, open label, multicenter trial Wexner *et al*[11] confirmed the effectiveness of NRM on improving FI in a large sample of 120 patients with 112 of them undergoing permanent implantation. The vast majority of patients (83%) reported significant improvement of FI according to the outcome measurement selected including 41% gaining complete anal continence, after a mean follow-up of 28 mo[11]. Since FI is a chronic disorders, Mellgren *et al*[12] reported on the same cohort after a mean follow-up of 3.1 years (range 0.2-6.1 years) with at least partial data set available in 64% of the patients. A significant decrement in episodes of incontinence was still reported by 86% of available patients with 41% regaining continence. A stable improvement in QOL score was also reported by patients [12]. To deepen the analysis a last observation carried forward statistics was performed showing a 78% success rate at 3 years. However, success rate would have drop to 59% at 3 years when considering all missing data as failures [12]. Historically, an anal sphincter disruption has been considered a contraindication to perform NRM which was not even considered in the presence of a relevant morphology alteration [7-9]. However, Chan *et al*[19] provided sound evidence *vs* this assumption in a comparative cohort study. The effectiveness of NRM in improving FI and QOL at one year was not significantly different in 21 patients with a disrupted external anal sphincter (81% persisting after previous sphincter repair) when compared to the outcome of 32 fecally incontinent patients with an intact anal sphincter [19]. These data were confirmed by a RCT comparing NRM with conservative treatment where many patients with defects in both the internal and external sphincters were included showing that NRM was approximately equally effective in those with or without sphincter disruption [15]. The therapeutic potential of NRM compared to conservative treatment in FI has also been reported in a number of mostly small sized study including patients with distinct pathological condition, among them rectal resection and pelvic irradiation [8,20,21]. In these distinct conditions dealt with in the following section, FI response rates may be lower, with approximately 50% of patients responding to temporary stimulation [20,21]. A recent meta-analysis by Tan *et al*[8] considered and reported on a total of 994 patients undergoing NRM with 665 permanently implanted confirming significant improvement on symptoms and QOL in FI. A disrupted anus was not a main determinant of outcome [8]. However, some criticisms on NRM outcome reports should be considered (Table I). Outcomes for NRM are often expressed as the proportion of patients receiving a permanent implant who continue to have at follow-up assessment a > 50% reduction in FI relative to baseline [8,11,12]. However, this likely over-estimates the efficacy of NRM compared to other treatments (*i.e.*, biofeedback therapy), where it is conventional to report effectiveness in terms of an intentention-to-treat (ITT) analysis [3]. To calculate the ITT response rate, one must include in the denominator all patients who received test stimulation (PNE). When this is done (Table 1), the responder rate ranges from 40% to 66% with a median of 59% compared to a median of 85% when only those who receive a permanent implant are included in the denominator [11,22,23]. In addition, some large studies did not provide the data to calculate the ITT responder rate ([13,16]). The response to temporary stimulation (PNE) ranges from 64% to 96%7 with a median of 87%10 reporting at least a 50% reduction in FI from baseline [8,22-24]. In a recent Danish study, a questionnaire was mailed to 127 FI patients with ongoing NRM to address subjective patients satisfaction and frequency of incontinence and 85% responded [25]. A total of 57.3% of the responders reported positively about NRM treatment [25], a percentage close to the calculated ITT response rate. In addition, satisfaction with treatment was closely related to pre-treatment frequency of incontinence, namely the more incontinent the patient was the more likely to report treatment dissatisfaction [25]. Finally, the effects of SNS are well sustained with 75% of those treated still reporting > 50% symptom reduction at approximately 7 years [26]. In a separate study Uludag *et al*[27] reported that 84% were still reporting > 50% FI reduction at 7 years. Switching off the sacral nerve stimulator at night might reduce the device associated expenses, but it is likely associated with a poor long term outcome [28].

***Distinct and rare conditions***

The efficacy of NRM has also been investigated in a number of distinct and rare conditions associated with FI including (1) double incontinence, (2) rectal resection, (3) pelvic radiotherapy, (4) anal sphincter atrophy and (5) spinal lesions. In these conditions FI is commonly deemed unresponsive to conservative treatment and poorly amenable to surgical intervention [2,3]. This consideration lead to mostly case report and small case series reporting on NRM treatment of FI with encouraging results, but no carrying forward to adequately powered and RCTs [9]. Notwithstanding that NRM to treat FI was developed by sporadic observations of symptom benefit in urge urinary incontinence, few studies have addressed the benefit of NRM in double incontinence [9]. Caramel *et al*[29] first reported on clinical questionnaires sent to 57 patients with double incontinence treated by permanent implantation with FI as main indication to NRM in 60% of them. About two third of patients responded with 49% of them reporting an improvement in both fecal and urine incontinence. Patients implanted for urinary incontinence as main indication were more likely to report full amelioration of both type of incontinence [29]. Recently, Faucheron *et al*[30] reported a single Center experience on 57 patients (54 women) who underwent PNE and permanent implantation for double incontinence of multiple etiology with a median follow-up of 62.8 mo. Improvement in both anal and urinary incontinence was addressed by dedicated scores with approximately 50% of patients reporting amelioration in both symptoms [30]. Quite surprisingly bladder related clinical improvement scored slightly lower than the bowel one. Re-intervention rate (29%) and complication rate (12%) were both relatively high [30]. Rectal resection for cancer and pelvic radiotherapy are conditions commonly associated with secondary severe alterations in bowel compliance [3]. Incontinence is predominant at night and mostly deemed “incurable” [2,3]. Two European Groups investigated the efficacy of NRM in these hard-to-treat conditions in small sized samples. Both studies reported PNE to be effective in improving continence in approximately half of those treated, but the efficacy of permanent implantation was not reported [20,21]. Atrophy of the anal sphincter is an additional hard-to-treat FI disease where NRM has been associated with clinical benefit in open trials. Santoro *et al*[31] have reported a single Center experience on 28 patients with MRI documented external anal sphincter atrophy of different severity undergoing permanent implantation for FI. A significant improvement in both FI score and QOL score were reported regardless of severity of sphincter atrophy [31]. This study provided indirect evidence *vs* improvement in anal sphincter function as relevant mechanism of action for NRM [31]. Finally, few studies evaluated the efficacy of NRM in the loss of normal bowel function due to nerve injury, neurological disease, or congenital defects of the nervous system, so called neurogenic bowel. Holzer *et al*[32] assessed clinical outcome in a cohort of 29 patients undergoing permanent implantation for FI of mixed neurological etiology including diabetes. The Authors claim that the vast majority of patients were symptomatically improved, but outcome parameters were ill defined [32]. Recently, an Italian group reported on the efficacy of NRM in improving symptoms of pelvic floor dysfunction in 23 patients suffering of incomplete spinal cord damage [33]. A significant improvement in FI was found in the majority of complainers, but the grouping of patients suffering of both constipation and FI makes hard to interpret the results [33].

**COST**

The costs of NRM are high when compared to conservative medical management, pelvic floor exercises and biofeedback therapy. Actual costs of NRM will vary widely from one country to another as well among different health insuring conditions. However, studies from three different countries have concluded that NRM is cost-effective when offset by the quality-adjusted life-years gained, and that it is likely to be reimbursed by government health programs [22,24,34,35].

**CONCLUSION**

In conclusion, Neuromodulation is effective treatment for fecal incontinence of diverse etiology. Encouraging results have also been reported for FI therapy in distinct and rare conditions, but no firm conclusion can be drawn about for the lack of both sized and randomized controlled trials. Neuromodulation is reported to benefit long term more than two third of FI patients undergoing permanent implantation by unknown mechanism. However, when analyzed by intention-to-treat analysis, the median responder rate drop down to 59% of those treated. NRM is a minimally invasive procedure. The most common serious adverse event is infection at the site of implant which occurs in approximately 3% and requires device explant in approximately 3% of all patients receiving permanent implants. Cost of treatment is high relative to conservative treatment and biofeedback but there are studies run in different countries suggesting NRM is cost-effective when offset by gains in quality adjusted years. However, RCTs comparing NRM to biofeedback therapy in FI would be advisable to solve the issue.

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**P-Reviewer** Santoro GA **S-Editor** Song XX **L-Editor E-Editor**

**Table 1 Effectiveness of neuromodulation in fecal incontinence**

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| **Ref.** | **Sample** | **Study design** | **Major findings** | **Adverse events** | **Comments** |
| Tjandra *et al*[9] | 120 patients with severe FI (solid or liquid FI >1/wk) were randomized to 2 groups. Of 60 randomized to test stimulation, 53 received permanent implants. Average age 63; >90% female. Sphincter defect or scar in 47% of both groups. | Single site RCT comparing NRM to optimal medical management. | 71% of permanently implanted patients (63% of randomized patients—ITT analysis) reported >50% reduction in FI episodes/week at 12 mo. FI episodes per week decreased from 9.5 to 3.1 in SNS group, and not at all in controls. All 4 QOL domains significantly improved in SNS. Anal squeeze pressures were unchanged. SNS significantly different from control on all outcomes. | Pain in 6%, seroma in 2%, and excessive tingling in vaginal region in 9%, but no septic complications. | Low complication rate and excellent outcomes may be related to this being a single-site study. |
| Wexner *et al*[11] | Multisite study. 133 received test stimulation; 120 (90.2%) qualified for permanent implant. Average age 60.5 yr; 92% females. Inclusion required >2 solid or liquid accidents/week for >6 mo and >12 mo post-partum. | Multisite cohort study in United States, Canada, and Australia. Hypothesis was that >50% would report >50 reduction in FI frequency at 12 mo compared to baseline. QOL and safety were secondary endpoints. | 73% of permanently implanted patients (66% of all undergoing test stimulation—ITT analysis) showed >50% reduction in FI episodes/week at 12 mo. FI episodes/week decreased from 9.4 at baseline to 1.9 at 12 mo. All 4 domains of the FIQOL improved significantly. An IAS defect predicted poorer outcome. | Pain in 25.8%, paresthesias in 12.5%, infection in 10.8% |  |
| Mellgren *et al* [12] | See Wexner (2010). 77 patients completed the 36 mo FU assessment | This reports the 36 mo outcomes for the Wexner (2010) study. | At 36 mo, 86% of 77 patients available for assessment, but only 55% of 120 enrolled patients, reported >50% reduction in FI. | Pain in 28%, paresthesia in 15%, infection in 10%. 5/120 required device explant and 2 required device replacement. | ITT analysis under-estimates efficacy because some patients were lost to FU for reasons unrelated to efficacy. |
| Michelsen *et al*[16] | 177 patients at single Danish hospital. Average age 60. 142 (80%) had positive PNE and 126 received NRM. | Uncontrolled case series. | In 107 of 111 who still had stimulator in place at 12 mo, Wexner score decreased in 87 (median decrease of 7) and was unchanged or worse in 20. No significant change in anorectal manometry. | 15 of 126 with permanent implant had device explanted. There were 2 infections requiring explant. | ITT analysis was not possible. Many patients were lost to FU. |
| Hollingshead *et al*[13] | 118 patients received PNE, 91 (77%) qualified for NRM; and 86 received NRM. | Uncontrolled case series. | For all 86, median FI episodes/week decreased from 8.5 to 1.3 and Wexner score decreased from 15 to 9. In 16% of patients reporting 50% reduction initially, efficacy was lost at median of 11.5 mo. | Broken leads in 2. Battery replacement in 7 at mean of 81 months. No other AEs reported. | ITT analysis not possible. |
| Altomare *et al*[23] | 94 patients from 6 hospitals underwent PNE, and 60 qualified for and underwent NRM. Average age 58, 83% females. | Uncontrolled case series. | Of 60 implanted, 2 died (unrelated) and 6 had devices explanted, leaving 52 for 5 year FU. At 5 years 37 (39% by ITT) had >50% decrease in FI frequency. Squeeze and resting pressures increased, maximum tolerated volume decreased. | AEs in 8 patients:  Electrode displacement in 8; pain in 3, allergic reaction in 1; myo-cardial infarct in 1; unrelated death in 2. | ITT success rate at 5 years was 40% after adjustment for 2 unrelated deaths. |
| Munoz-Duyos *et al*[24] | Spanish study of 47 patients who received PNE, of whom 29 (62%) received NRM,. PNE was ineffective in 16 and 3 had technical failures. | Uncontrolled case series with median 3 years FU. Cost analysis was primary focus. | At last FU, 14 were continent and 11 had >50% reductions in FI frequency. QOL significantly improved. Total direct costs for NRM were 371,434 euros, estimated to be 16,181 euros per quality adjusted life year. No improvement in anal canal pressures. | 8 patients experienced pain but none required explant. | ITT response rate was 53.2%. |
| Dudding *et al*[22] | British study of 70 patients who received PNE, of whom 61 had >50% reduction. At analysis, 51 had received permanent implants, and FU was available for 48. These patients may also be included in the Hollingshead (2011) report. | Uncontrolled case series with median 24 mo FU. Primary focus was cost effectiveness. Direct and indirect costs were estimated by theoretical model of services required rather than on actual costs. | At 24 month FU, 41 of 48 with long-term FU (85.4%) had >50% reduction. Direct costs were estimated at 9795 pounds for SNS compared to 2529 pounds for conservative treatment. The estimated incremental cost effectiveness ration was 25070, which is below national guidelines. | 10/48 had complications including 2 wound infections, 1 lead migration, 5 pain, 2 device failures. | ITT response rate was 58.6%. Cost analysis was based on theoretical/ imputed data rather than real costs. |
| Chan *et al*[19] | 60 consecutive patients underwent PNE and 53 received NRM. These were separated into 21 with EAS defect *vs* 32 with intact EAS. One surgeon did all surgeries. | Prospective cohort study comparing those with EAS defect to those with intact sphincter. | There was a trend for patients with EAS defect to have worse incontinence and poorer squeeze pressures at baseline and FU, but not significant. Outcomes were similar: At 12 mo FU 68.8% with sphincter disruption *vs* 72.0% with intact sphincter had >50% reduction in FI. No differences in anal manometry or QOL outcomes. | Seroma in 1/53; pain in 3/53. No AEs required explant. | Strong support for hypothesis that NRM is equally effective in patients with EAS defects. ITT responder rate for combined group was 63% |
| Michelsen *et al*[28] | 20 patients randomized; 19 had complete data. | Randomized prospective cross-over comparing NRM on continuously for 3 wk to NRM on only during waking hours for 3 wk. | Wexner and St Mark’s incontinence scores and frequency of soiling were significantly worse during device off period. However, FI frequency was not significantly different between conditions. | AEs were not reported | Not directly relevant to efficacy of NRM. |
| Leroi *et al*[18] | 34 consecutive FI patients (31 females) considered, 27 eventually studied, 24 completed the trial | Randomized, double-blind, cross-over, controlled trial. All 27 patients underwent NRM then randomized in a double-blind crossover design to stimulator ON *vs* stimulator OFF for 1-mo interval. Patients while blinded choose to meet the final period of 3 mo ON or OFF | Cleveland Clinic Continence score, frequency of FI and urgency, delay in postponing defecation, subjective feeling of improvement, anal physiology, QOL score all significantly improved in the ON interval compared to the OFF interval | 10 out of initial 34 reported AE, 4 device explantations: 3 for pain and 1 for infection | First RCT to show effectiveness of NRM compared to Placebo, Underpowered sample |

NRM: Neuromodulation; FI: Fecal Incontinence; FU: Follow-up; RCT: Randomized controlled trial; QOL: Quality of life; AE: Adverse events; PNE: Percutaneous nerve evaluation; ITT: Intention-to-treat; EAS: External anal sphincter.