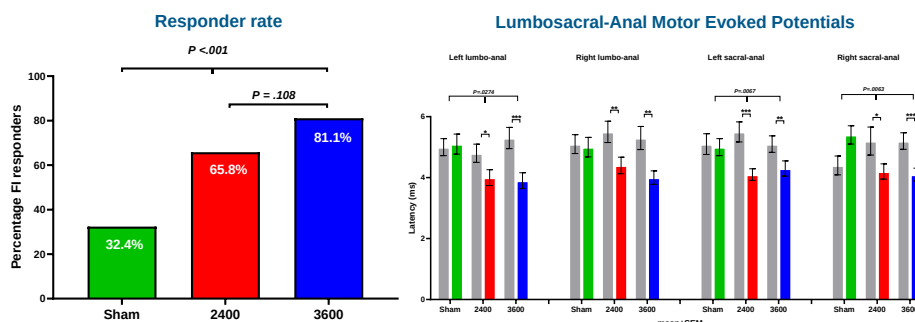


Randomized Sham-Controlled Trial of Translumbosacral Neuromodulation Therapy for Fecal Incontinence

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Translumbosacral Neuromodulation Therapy (TNT) in Fecal Incontinence (FI): Randomized Trial



TNT, a novel, non-invasive, outpatient treatment was significantly more efficacious than sham in improving symptoms and neuropathy and was safe and well-tolerated in FI patients.

Gastroenterology

BACKGROUND & AIMS: Fecal incontinence (FI) is a multifactorial disorder that lacks effective, disease-modifying treatments. We investigated the efficacy and safety of translumbosacral neuromodulation therapy (TNT), a novel noninvasive treatment targeting neuropathy, in a multicenter, double-blind, randomized sham-controlled trial. **METHODS:** FI patients (≥ 1 leakage/wk) were randomized to receive TNT (1 Hz) with either 2400 or 3600 repetitive magnetic stimulations or sham stimulations at 4 lumbosacral sites, weekly for 6 weeks. Daily FI episodes and bowel symptoms were assessed with prospective stool diaries. Outcomes included a $\geq 50\%$ decrease in weekly FI episodes (primary), FI Severity Index, quality of life, anorectal function, and neurophysiology. **RESULTS:** Of 109 patients randomized, there were 25 of 38 (65.8%) responders in the 2400 group, 30 of 37 (81.1%) responders in the 3600 group, and 11 of 34 (32.4%) responders in the sham group (odds ratio (95% confidence interval) for 2400 vs sham: 3.91 (1.48–10.91); for 3600 vs sham: 8.53 (2.96–27.47); 3-way analysis of variance $P \leq .001$). FI Severity Index scores improved significantly in the TNT groups compared with sham ($P = .02$). FI quality of life domains improved in TNT groups compared with baseline ($P = .002$) but not between groups and in sham group. Lumbo-anal, sacro-anal, lumbo-rectal, and sacro-rectal nerve conduction latencies ($P < .04$) and anal squeeze pressures ($P < .05$) improved in the TNT groups when compared

with sham. No treatment-related serious adverse events were reported. Two patients in each group reported back pain, and 1 patient each in the 2400 and 3600 groups reported tingling and urinary urgency. **CONCLUSIONS:** TNT treatments with 2400 and 3600 magnetic pulses showed superior efficacy in improving FI and bowel symptoms when compared with sham treatment and was safe and well tolerated. (ClinicalTrials.gov: [NCT03899181](https://clinicaltrials.gov/ct2/show/study?term=NCT03899181))

Keywords: Translumbosacral Neuromodulation Therapy; Fecal Incontinence; Treatment; Neurophysiology.

Abbreviations used in this paper: CI, confidence interval; FI, fecal incontinence; FI-QOL, Fecal Incontinence Quality of Life; FISL, Fecal Incontinence Severity Index; MEP, motor evoked potential; OR, odds ratio; TAMS, translumbosacral anorectal magnetic stimulation; TNT, translumbosacral neuromodulation therapy.

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Fecal incontinence (FI) is a distressing problem with a global prevalence of 8% in community-dwelling adults.¹ It predominantly affects women, older individuals, and nursing home residents.¹ It impairs quality of life² and has a major impact on health care burden.³ A critical barrier to progress in the treatment of FI is the lack of randomized controlled trials, and absence of mechanistically based, noninvasive therapies that modify its pathophysiology.

A significant factor in the pathogenesis of FI is lumbar and sacral plexus neuropathy affecting the anorectum.^{4,5} Neuropathy may induce anal sphincter weakness, and anorectal sensori-motor dysfunction causing FI. The neurologic innervation of the anorectum is however complex and comprises of at least 5 overlapping networks involving the sympathetic, parasympathetic and somato-motor nerves that are enmeshed within the pelvic floor organs,⁶ making them vulnerable to trauma from multiple risk factors such as obstetric and surgical injuries, back injury, diabetes, and neurologic conditions.^{5,7} Advanced neurophysiology testing using translumbosacral anorectal magnetic stimulation (TAMS) has demonstrated significant neuropathy in FI patients.⁵

By remedying the underlying neuropathy, neuromodulatory treatments may improve FI.^{4,8} In this context, unilateral electrical sacral nerve stimulation has shown benefit in open-label short-term and long-term studies and in 3 randomized controlled trials and is approved for FI treatment.⁸ However, its mechanism of action is unknown, although some studies have reported improvements in rectal sensation.⁸ Also, sham-controlled trials demonstrate a clinically meaningful improvement with sham stimulation.⁹

Another novel noninvasive method is translumbosacral neuromodulation therapy (TNT) that delivers focal magnetic energy transcutaneously to all lumbo-sacral nerves that regulate anorectal function.^{4,10} This builds on the concept of repetitive transcranial magnetic stimulation that is effective in treatment-refractory depression¹¹ and post-stroke dysphagia.¹² In a randomized study of 1 Hz, 5 Hz, and 15 Hz TNT, the optimal magnetic stimulation frequency for inducing improvement in FI symptoms was 1 Hz.⁴ Additionally, 1 Hz improved neurophysiology,¹³ suggesting that the effects of TNT are mediated through neuroplasticity. However, this was not a sham-controlled study.

Our hypothesis is that TNT treatment with repetitive magnetic stimulations is superior to sham treatment in improving FI symptoms and that it provides a multidimensional therapeutic benefit. Our aims were to test the efficacy, safety, and optimal dose of TNT when compared with sham treatment in a randomized, multicenter trial of FI patients.

Methods

Study Design

We conducted a phase 3 multicenter, double-blind, parallel-group, sham-controlled, 3-arm clinical trial at 2 academic centers in the United States between June 5, 2019 and April 3,

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

A significant factor in the pathogenesis of fecal incontinence (FI) is lumbar and sacral plexus neuropathy affecting the anorectum. Translumbosacral neuromodulation therapy (TNT) is a novel treatment for FI using repetitive magnetic stimulations designed to remedy neuropathy.

NEW FINDINGS

In a double-blind, sham-controlled, randomized trial, 2400 or 3600 repetitive magnetic stimulations significantly improved FI symptoms, FI severity, quality of life, lumbosacral plexus neuropathy, and anal sphincter function. TNT treatment was safe and well-tolerated with 94% compliance and no significant adverse events.

LIMITATIONS

Although efficacious in the short-term, the durability of TNT needs further assessment in a longer-term, sham-controlled trial. Although higher dose of 3600 pulses had more responders than 2400, this difference was not significant owing to sample size.

CLINICAL RESEARCH RELEVANCE

Our study demonstrates that TNT, a noninvasive, outpatient-based treatment program using magnetic stimulation, effectively improves FI symptoms and its underlying pathophysiology through neuromodulation. Whether higher doses or more frequent administration of magnetic stimulations, especially in a community setting, improves outcomes merits further study.

BASIC RESEARCH RELEVANCE

Our findings highlight the need for further research into the basic neurophysiological mechanisms and the role of neuroplasticity in improving anorectal function after electrical, magnetic, and other neuromodulatory techniques.

2024 to assess the efficacy and safety of TNT in patients with FI. All participants provided written informed consent approved by the institutional review board (IRB No. 1303352). ([ClinicalTrials.gov](https://clinicaltrials.gov) ID [NCT03899181](https://clinicaltrials.gov/ct2/show/study?term=NCT03899181).)

Participants

Adult ambulatory patients with recurrent episodes of FI for 6 months that were nonresponsive to diet, fiber, antidiarrheals, and Kegels exercise, and absence of colonic mucosal disease (colonoscopy), and reported at least 1 episode of solid or liquid FI/wk on a 2-week prospective electronic stool diary were included. Patients were excluded if they had severe diarrhea (≥ 6 liquid stools/d, Bristol Stool Form Scale [BSFS] ≥ 6), were on opioids or pregnant, active depression, severe comorbid illnesses including cardiac disease or renal failure, previous abdominal surgery (except cholecystectomy, appendectomy, hysterectomy, and Nissen fundoplication), neurologic diseases (eg, epilepsy and strokes), impaired cognizance, nursing home residents, metal implants, pacemakers, pelvic

radiation, radical hysterectomy, ulcerative and Crohn's colitis, rectal prolapse, anal fissure/abscess, or previous anal surgery such as anal atresia or fistula or inflamed hemorrhoids. Baseline antidiarrheals, bile sequestrants, or fiber supplements were permitted throughout the study, but no additional new therapies for bowel problems were allowed during the study. Demographic data were collected through a standardized form using self-report. Women of child-bearing age underwent pregnancy testing at baseline and during each visit.

Randomization and Masking

The biostatistician generated a randomization list using permuted block size of 6 to ensure balance among the 3 treatment arms and across centers. Serially numbered sealed envelopes containing the assignments were prepared by the biostatistician and kept with the Data Coordinating Center coordinator. Once a patient became eligible, the research assistant at each site contacted the Data Coordinating Center coordinator, who provided the subject's randomization. This research assistant also performed the repetitive magnetic stimulation procedure on each participant but was not involved in the data analysis. All patients and investigators performing clinical outcome assessments were masked to the treatment allocation. To achieve masking, all patients had an identical equipment setup in the room including the use of sham repetitive coil that looks identical and mimics the auditory and vibratory cues and physical properties of the active coil with a built-in shield to reduce magnetic diffusion. Hence, it delivers significantly less magnetic energy at 1 Hz.

Procedures

Participants kept a prospective electronic stool diary for a 2-week period (Figure 1) before randomization in which they recorded daily stool patterns, number of incontinence episodes, stool consistency using the BSFS, FI patients severity (1 = mild, 2 = moderate, 3 = excessive), stool urgency, and medications.¹⁴ Also they completed, the Fecal Incontinence Severity Index (FISI),¹⁵ Fecal Incontinence Quality of Life (FI-QOL),¹⁶ and subject global assessment scale (rating, 0–100),⁴ both at baseline and end of study. The safety and tolerability were assessed after 6 treatment sessions using a 20-item device and treatment tolerability questionnaire designed to avoid unidirectional bias and comprising 3 domains (safety, tolerability, and functionality) and were scored as either agree, neutral, or disagree. They also underwent high-resolution anorectal manometry,^{4,7} and TAMS test⁵ at baseline and after treatment, and anal ultrasound⁷ at baseline. High-resolution anorectal manometry was performed by placing a probe into the anorectum (ManoScan, Medtronic, Ireland) and using standard methods.¹⁷ Anal ultrasound (BK Medical Holding Company Inc., UK) assessed sphincter defects.⁷ TAMS was performed by placing a flexible probe with 2 pairs of bipolar steel ring electrodes (Gaeltec Ltd, Isle of Skye, UK) into the rectum. Single pulses of magnetic stimulations were given transcutaneously at bilateral lumbar and sacral sites by using a 90-mm coil and magnetic generator (Magstim Rapid2, Whitland, UK). The motor evoked potential (MEP) latencies were used to assess lumbo-sacral neuropathy at 8 sites.⁵

The study consisted of 8 visits that included screening, randomization, and 6 treatment visits (Supplementary

Figure 1). Based on randomization, the TNT group received repetitive magnetic stimulations at 1 Hz frequency using either 600 or 900 magnetic pulses at each site (total dose = 2400 or 3600) using a 70-mm double air film self-cooling coil (Magstim, UK).⁴ The sham group received 600 pulses at each site, using a 70-mm self-cooling sham coil (Magstim, UK) at 1 Hz (total = 2400). The air-cooled sham coil looks identical and provides similar auditory and vibratory sensations as evoked by the active coil. With the subject lying prone, the active or sham coil was positioned randomly over 1 of 4 sites and held in place by a coil fixator. The magnetic pulses were delivered in 2 trains transcutaneously at the bilateral lumbar (L2-L3) and sacral (S2-S3) sites (Supplementary Figure 2) that approximately corresponded to the lumbar and sacral plexus nerves supplying the anorectum.^{5,6} The precise location of each site together with the motor threshold intensity for magnetic stimulation was identified using the TAMS test.⁵ At each site, the repetitive magnetic pulses were administered with a 3-minute interval between the 2 trains and a 5- to 10-minute interval between each of the 4 sites. Patients were monitored for any adverse events. All patients maintained a daily electronic stool diary throughout the trial. Patients and investigators were blinded to interventions and data analysis except the investigator performing TNT treatments.

Outcomes

The primary outcome measure was the FI responder rate and this was defined as the proportion of patients demonstrating 50% or greater reduction in FI episodes at the end of 6 weeks when compared with their baseline period.^{4,7,18} Secondary outcome measures included changes in stool frequency, stool consistency (BSFS, 1–7), and $\geq 75\%$ reduction in FI episodes or no leakage when compared with baseline. FI severity was assessed using FISI¹⁵ and subject global assessment, quality of life using FI-QOL scale,¹⁶ and anorectal function using TAMS and manometry. The results obtained before and after treatment and the differences between the sham and TNT groups were compared. Adverse events were documented.

Statistical Analysis

The study was powered to examine the differences in the primary outcome variable (the proportion of FI responders) for the 3 groups. Assuming responder rates of 20%, 65%, and 82% for the sham, 2400, and 3600 groups, respectively, and based on previous dose response study,⁶ a total of 108 subjects (36 per group) was planned to achieve at least 80% power.

Data were analyzed using an intention-to-treat analysis. If a patient withdrew from the study, their last observation was carried forward. Descriptive statistics were calculated for all variables of interest in each group: TNT 2400, TNT 3600, and sham. Normality of data was assessed using the Shapiro-Wilk test. For non-normal variables, a nonparametric Wilcoxon rank-sum test was performed. For the primary outcome variable ($\geq 50\%$ reduction in FI episodes) and other qualitative outcome variables, a Fisher exact test was used to determine the differences in proportions between the 3 groups of the study. The rate of change in number of FI episodes was assessed using a log-linear relationship over time using the formula ($\text{Percent change} = \alpha_{Tt} + \beta_{Tt} * \log(\text{Week} + 1)$) where

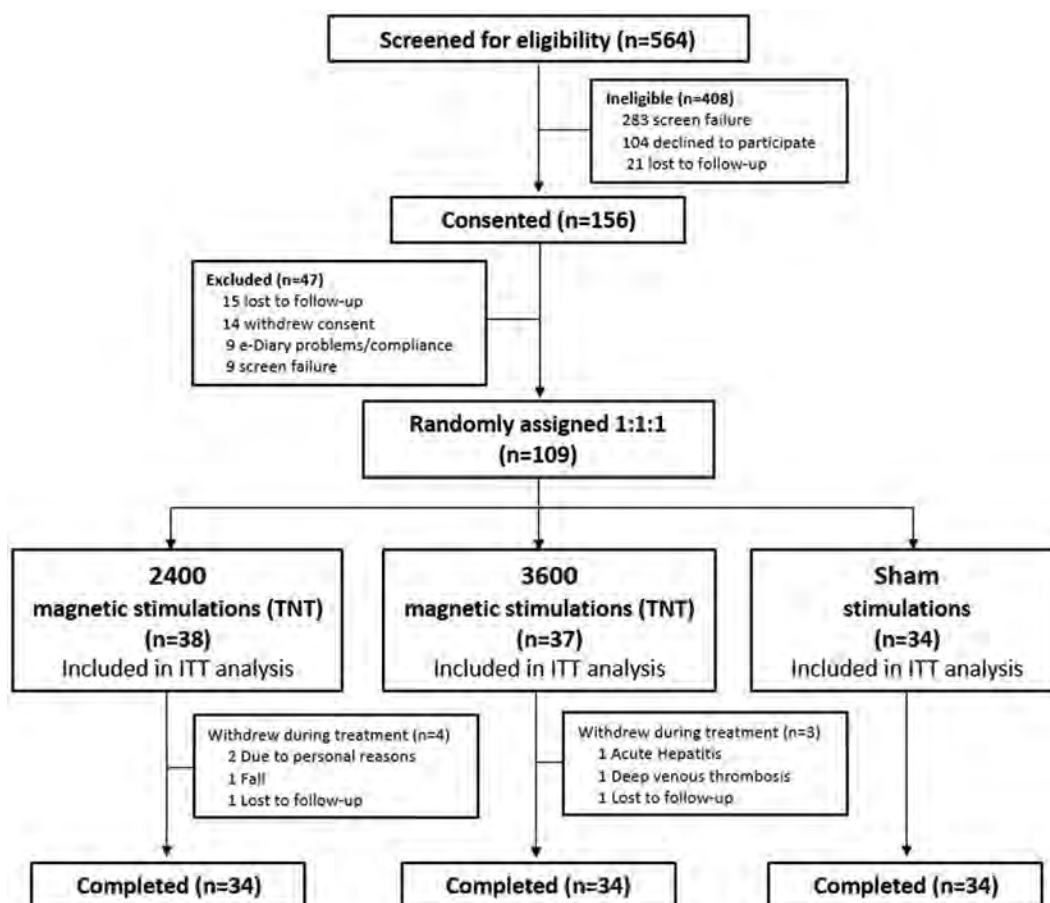


Figure 1. Consort flow diagram of study participants. ITT, intention to treat.

α and β represent intercept and slope coefficients and T_{rt} represents treatment groups. A paired t test was used to examine changes from baseline for various quantitative outcome measures. A 1-way analysis of variance test was used to examine changes from baseline between the 3 groups (2400, 3600, and sham). Within each group, outcomes were compared between baseline and post-treatment. A t test was used to compare baseline MEP latencies with healthy historical controls and also between baseline and post-treatment latencies between the groups. No imputation of data was performed as the analysis was performed with an intent-to-treat. Data analyses were performed using R version 4.2.2. An alpha level of .05 was used to assess the significance of each parameter. Wherever appropriate, multiplicity adjustments were performed for all data variables using false discovery rate approach. A Data Safety Monitoring Board oversaw the study.

Results

Patients

We screened 564 patients with FI of whom 156 consented and 109 patients were randomized to 1 of 3 treatment groups (Figure 1). After consent, 9 patients were excluded because their FI episodes improved significantly with conservative medical management including antidiarrheals and Kegels exercises and were therefore no longer

eligible. The demographics, baseline symptoms, number of FI episodes and its severity, FI type, and anorectal structural and physiological characteristics showed no differences between the 3 patient groups (Table 1). Nearly 90% of patients had evidence of neuropathy at one or more lumbosacral sites with no differences between groups (Supplementary Table 1).

Primary Efficacy Outcome

The FI responder rate (primary outcome) demonstrated statistically significant improvement in patients who received 3600 and 2400 TNT treatments when compared with the sham treatment ($P < .001$) (Figure 2A). For the 2400 group vs sham, the odds ratio (OR) is 3.91 (95% confidence interval [CI], 1.48–10.91; for 3600 group vs sham, the OR is 8.53 (95% CI, 2.96–27.47). There was no difference between 2400 and 3600 groups (OR, 0.46; 95% CI, 0.15–1.31).

Secondary Efficacy Outcomes

The 75% FI responder rate was significantly higher in TNT groups compared with sham (Figure 2B). The number of days without FI significantly increased in the TNT groups compared with sham and baseline (Table 2). The number of weekly FI episodes decreased significantly in the TNT groups compared with sham and baseline. The percentage

Table 1. Baseline Demographic, Clinical, Manometric, Structural, and Neurophysiological Characteristics of FI Patients

Characteristic	Sham (N = 34)	2400 (N = 38)	3600 (N = 37)
Age (y)	63.5 (59.9–67.3) ^a	64.1 (60.6–67.5) ^a	65.5 (61.9–68.2) ^a
Female sex, no. (%)	29 (85.3)	29 (76.3)	28 (75.7)
Duration of FI symptoms (y)	5.3 (3.8–6.8) ^a	5.2 (3.1–7.3) ^a	6.8 (4.0–9.7) ^a
Race, no. (%)			
White	21 (61.7)	26 (68.4)	27 (73.0)
Black	9 (26.5)	11 (28.9)	8 (21.6)
Other	4 (11.8)	1 (2.6)	2 (5.4)
Stool frequency/wk	12.0 (9.6–14.2) ^a	13.8 (11.6–15.9) ^a	16.2 (13.3–19.1) ^a
No. of FI episodes/wk	6.6 (4.3–8.8) ^a	8.3 (6.6–9.9) ^a	7.7 (5.7–9.5) ^a
Stool consistency (BSFS)/wk	4.7 (4.2–5.0) ^a	4.8 (4.3–5.2) ^a	5.0 (4.6–5.4) ^a
No. of subjects with passive FI (%)	15 (44.1)	11 (28.9)	14 (37.8)
No. of subjects with urge FI (%)	14 (41.2)	17 (44.7)	11 (29.7)
No. of subjects with both passive/urge FI (%)	5 (14.7)	10 (26.3)	12 (32.4)
No. of women with history of obstetric injury (%)	20 (68.9)	22 (75.9)	15 (53.6)
Anal resting pressure (mm Hg)	52.5 (45.0–60.0)	57.8 (47.4–68.1)	56.7 (48.8–64.5)
Maximum squeeze pressure (mm Hg)	135.0 (111.0–158.8)	127.7 (112.3–142.9)	133.0 (110.0–155.8)
No. of subjects with anal sphincter defects (%)	17 (50.0)	19 (50.0)	14 (37.8)
EAS defect (%)	15 (44.1)	18 (47.4)	14 (37.8)
IAS defect (%)	7 (20.6)	10 (26.3)	7 (18.9)
No. of subjects with lumbosacral plexus neuropathy (%)	31 (91.2)	34 (89.5)	35 (94.6)

EAS, external anal sphincter; IAS, internal anal sphincter.

^aMean (95% CI).

change in weekly FI episodes significantly improved in the TNT groups compared with sham group starting as early as week 1 (Figure 3). The weekly stool frequency decreased significantly between the 3 groups ($P = .04$) as well as in the 2400 ($\Delta = 2.58 \pm 2.29$; $P = .03$) and 3600 ($\Delta = 5.19 \pm 1.96$; $P < .001$) groups compared with baseline, but not in the sham group ($\Delta = 1.56 \pm 1.77$). There was a significant decrease in the mean stool consistency in the 3600 group compared with sham ($\Delta = 0.27 \pm 0.33$; $P < .001$) and baseline ($\Delta = 0.67 \pm 0.33$). The percentage of FI episodes per week without any awareness of stooling sensation decreased significantly in the 2400 and 3600 groups when compared with baseline ($P < .03$) but not in the sham group. The percentage of FI episodes per week associated with urgency decreased in the 2400 and 3600 groups when compared with sham and baseline ($P = .02$). Two patients each in the sham and 2400 group, and 3 patients in the 3600 group took loperamide. Also, 1 patient in each of the 3 groups took bile acid sequestrant. There was no difference in the concomitant medication use between the 3 groups during the study, and excluding these patients did not affect the trial outcome.

The baseline FISFI score decreased significantly in the 2400 ($\Delta = 8.63 \pm 2.97$) and 3600 ($\Delta = 5.56 \pm 3.84$) groups

when compared with sham ($\Delta = 1.45 \pm 3.24$; $P = .02$) and within each TNT group (Table 2). The subject global assessment (satisfaction) score increased significantly in the TNT groups when compared with sham ($P < .03$) and in all 3 groups when compared with baseline (Table 2). Although the 4 FI-QOL domains were not different between the 3 groups, there was significant improvement in the 2400 and 3600 groups when compared with baseline ($P < .02$) but not in the sham group (Table 2).

The baseline MEP latencies were similar across groups but abnormally prolonged at all sites when compared with historical healthy controls⁵ (Supplementary Table 1), suggesting significant lumbosacral neuropathy. After TNT, the latencies for the bilateral lumboanal and sacroanal MEPs decreased significantly in the 3600 and 2400 groups when compared with the sham group, except the right lumboanal MEP, and when compared with baseline (Figure 4). Similarly, the latencies for bilateral lumborectal MEPs decreased in the TNT groups compared with sham and baseline. The anal maximal squeeze pressure and sustained squeeze pressure significantly increased in the 2400 ($\Delta = 34.19 \pm 13.67$; $P < .001$) and 3600 ($\Delta = 15.19 \pm 14.42$; $P = .04$) groups when compared with baseline, and the sham group ($\Delta = 0.05 \pm 14.63$; $P < .04$; Supplementary Table 2).

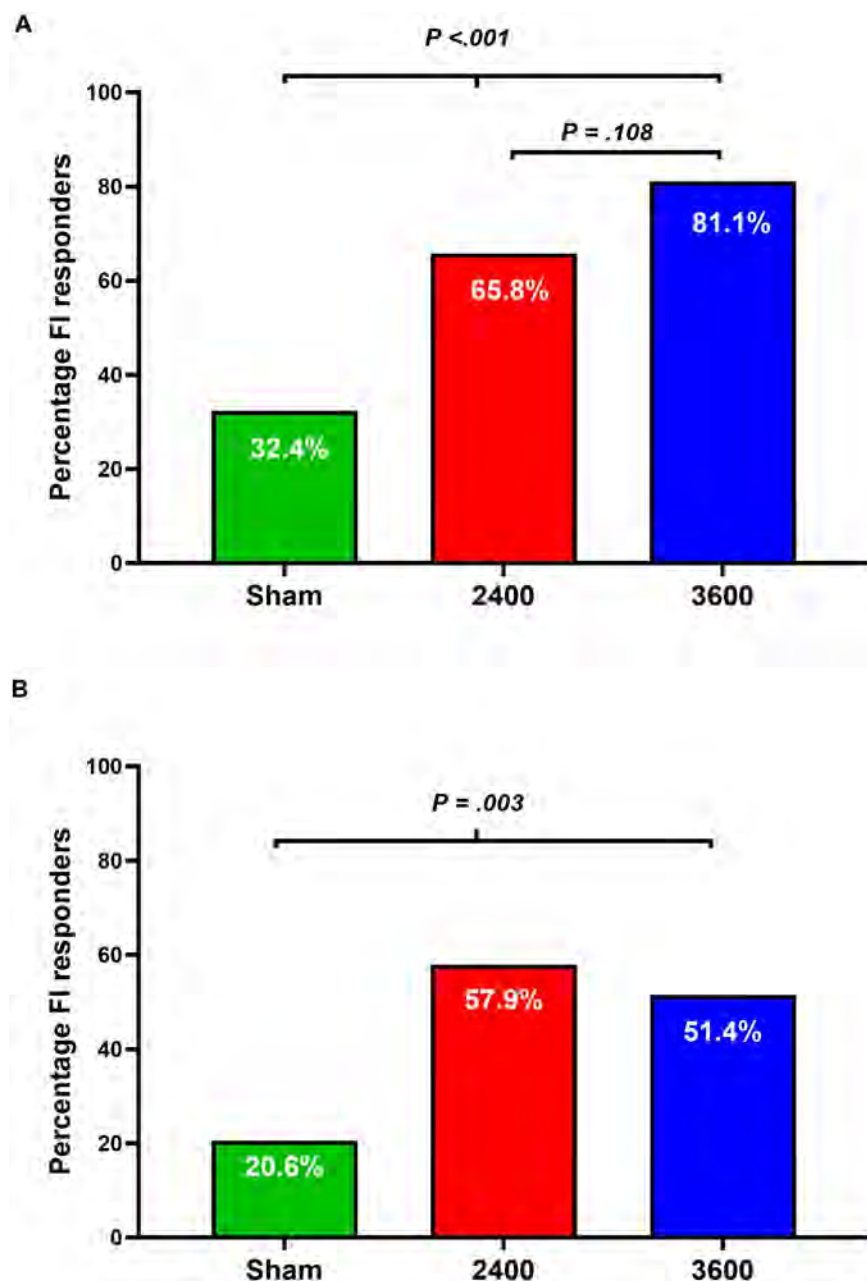


Figure 2. (A) Proportion of patients with 50% or greater reduction in FI episodes (primary outcome measure) after TNT treatment. (B) Proportion of patients with 75% or greater reduction in FI episodes (75% responder rate) after TNT treatment.

Safety Outcomes

There were 3 serious adverse events requiring hospitalization; 1 patient (2400 group) had a fall, 1 patient each (3600 group) had urosepsis and viral hepatitis (Table 3) and all were adjudicated as unrelated to the TNT treatment. Transient back pain was reported by 2 patients in each treatment group. Also, tingling or numbness, and urinary urgency were reported by 1 patient each in the TNT groups. Two patients had deep vein thrombosis (3600 group), 1 of whom had history of deep vein thrombosis with Lupus syndrome and the other received stem cell therapy for recently diagnosed osteoarthritis. Other adverse events were mostly similar between the groups. The Device and

Treatment Tolerability Questionnaire evaluated 7 questions on safety, and no differences were reported between sham and TNT groups (Supplementary Figure 3); 6 questions assessed patient tolerance and 75% reported good tolerability across all 3 groups, and 7 questions assessed functionality, and were rated similarly across groups with 75%–85% of patients recommending this treatment to others.

Discussion

In this randomized sham-controlled trial, TNT with either 2400 or 3600 repetitive magnetic stimulations was superior to sham stimulations in improving FI and restoring bowel control in patients with moderately severe FI who on average

Table 2. Effects of TNT and Sham Treatment on Bowel and FI Symptoms, and on FI Severity and Quality of Life Domains (Mean [95% CI])

	Sham (N = 34)			2400 (N = 38)			3600 (N = 37)			<i>P</i> ^a
	Baseline	Post-treatment	Δ	Baseline	Post-treatment	Δ	Baseline	Post-treatment	Δ	
No. of days with no FI episodes/wk	2.2 (1.5–2.7)	2.6 (1.7–3.3)	0.4 (–0.2, 1.0)	1.4 (0.8–1.9)	3.5 (2.7–4.3)	2.1 (1.3, 3.0)	2.0 (1.4–2.5)	3.6 (2.9–4.2)	1.6 (0.9, 2.2)	.02
% of patients with no FI episodes/wk	8.8			32.4			35.3			.001
Stool frequency/wk	12.0 (9.6–14.2)	10.4 (8.8–11.9)	1.6 (–0.2, 3.3)	13.8 (11.6–15.9)	11.2 (9.0–13.4)	2.6 (0.3, 4.9)	16.2 (13.3–19.1)	11.1 (9.0–13.0)	5.2 (3.2, 7.1)	.04
No. of FI episodes/wk	6.6 (4.3–8.8)	4.6 (2.9–6.2)	2.0 (0.9, 3.0)	8.3 (6.6–9.9)	3.5 (2.0–5.0)	4.8 (3.2, 6.4)	7.5 (5.7–9.5)	2.8 (1.5–4.1)	4.7 (3.2, 6.2)	.02
Stool consistency/wk	4.7 (4.2–5.0)	4.4 (3.9–4.9)	0.3 (–0.1, 0.3)	4.8 (4.3–5.2)	4.5 (4.1–4.8)	0.3 (0, 0.7)	5.0 (4.6–5.4)	4.4 (3.8–4.8)	0.7 (0.3, 1.0)	.28
No. of gas leakage/wk	6.5 (4.4–8.5)	4.7 (3.0–6.4)	1.8 (0.1, 3.4)	9.5 (7.0–11.8)	6.3 (4.0–8.6)	3.1 (0.8, 5.4)	5.2 (3.7–6.6)	3.4 (1.7–5.0)	1.8 (0.5, 3.1)	.54
% of FI episodes without awareness	37.8	21.0	17.8	32.8	18.4	14.4	46.7	24.8	21.9	.79
% of FI episodes with strong urgency	27.3	33.0	–5.7	36.4	21.4	15.0	27.6	7.3	20.3	.02
FISI	35.2 (31.6–38.7)	33.7 (30.1–37.3)	1.4 (–1.9, 4.8)	38.5 (35.6–41.3)	29.8 (26.0–33.7)	8.6 (5.7, 11.6)	37.2 (33.6–40.7)	31.7 (26.4–36.8)	5.6 (1.5, 9.6)	.02
SGA (VAS)	57.7 (51.5–63.7)	47.4 (41.3–53.4)	10.2 (2.9, 17.6)	65.7 (60.6–70.8)	40.7 (32.3–48.9)	25.1 (17.0, 33.2)	64.6 (58.1–70.9)	46.9 (38.5–55.3)	17.6 (10.6, 24.7)	.03
Quality of life										
Coping	2.0 (1.7–2.3)	2.1 (1.8–2.3)	–0.1 (–0.3, 0.1)	1.8 (1.5–2.0)	2.1 (1.8–2.3)	–0.3 (–0.5, –0.1)	1.8 (1.5–2.0)	2.1 (1.7–2.3)	–0.3 (–0.5, 0.0)	.73
Lifestyle	2.6 (2.3–2.9)	2.8 (2.4–3.1)	–0.2 (–0.3, 0.0)	2.3 (1.9–2.5)	2.6 (2.2–2.8)	–0.3 (–0.5, –0.1)	2.4 (2.0–2.7)	2.6 (2.2–2.9)	–0.2 (–0.4, –0.1)	.73
Depression	2.7 (2.4–3.0)	2.9 (2.6–3.1)	–0.2 (–0.3, 0.0)	2.6 (2.3–2.9)	2.9 (2.6–3.1)	–0.3 (–0.4, –0.1)	2.7 (2.4–3.0)	3.0 (2.7–3.2)	–0.2 (–0.4, –0.1)	.73
Embarrassment	2.0 (1.7–2.3)	2.1 (1.8–2.4)	–0.1 (–0.4, 0.1)	2.0 (1.7–2.2)	2.4 (2.0–2.6)	–0.4 (–0.6, –0.1)	1.9 (1.6–2.1)	2.3 (1.9–2.6)	–0.4 (–0.6, –0.2)	.73

SGA, subject global assessment; VAS, visual analog scale.

^a*P* represents overall difference among groups.

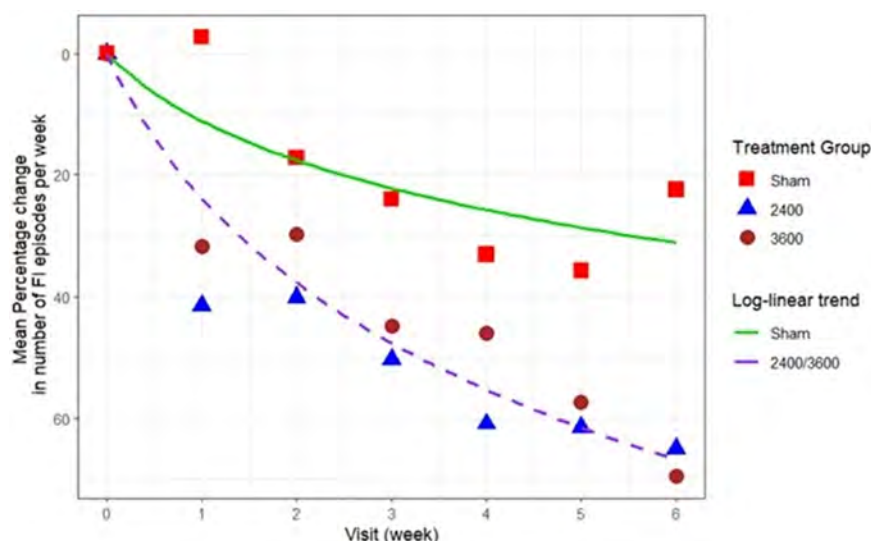


Figure 3. Effects of TNT and sham treatment on percentage change in weekly FI episodes.

had 7 incontinent episodes/week. We found a significantly greater percentage of responders at 81% (3600) and 66% (2400), respectively, in the TNT groups when compared with the sham group (32%), with a significant reduction in FI episodes starting as early as 1 week. Additionally, a greater proportion of patients receiving TNT demonstrated a 75% or more reduction in FI episodes when compared with the sham group. Overall, 93.5% of patients adhered to their assigned treatments suggesting excellent compliance and acceptability.

Among the TNT groups, FI improvement was further substantiated by other quality metrics such as the FI severity scores. Further, we observed a significant reduction in the occurrence of embarrassing problems such as urgency to rush to the toilet or in the proportion of FI episodes without awareness. The FI-QOL showed clinically meaningful¹⁶ improvements across all 4 domains in the TNT groups when compared with baseline but not in the sham group and between the groups. Thus, after TNT, key drivers for FI, such as emotional and social well-being, loss of self-dignity, and stool urgency,^{3,7} significantly improved.

Additionally, TNT also improved objective metrics. Lumbosacral neuropathy, a key pathophysiological mechanism for FI improved in both TNT groups as evidenced by shortened MEP latencies when compared with the sham group and baseline values. The demonstration of mechanistic improvements is important as previously only subjective endpoints such as adequate relief of symptoms¹⁹ were used for assessing FI improvement. Also, until recently objective assessment of neuropathy has been challenging, especially given the 5 overlapping sources of anorectal neuronal innervation.⁶ The TAMS test has, however, provided a comprehensive tool and the demonstration of significant changes post-treatment attests to its superiority over other tests.⁵

The therapeutic effect of TNT is likely mediated by neuroplasticity, which is the inherent ability of neurons to regrow and reconnect in response to repetitive stimulation as demonstrated by peripheral and central neuroplastic changes in human^{13,20} and animal studies.²¹ The repetitive

stimulations increase motor neuron excitability in the spinal cord improving conduction and promoting long-lasting effects via gamma amino butyric acid and other networks.²² Low-frequency magnetic stimulations may be more effective in inducing neuroplasticity in the peripheral neural circuitry as evidenced by improvements in visceral pain,¹⁰ FI,⁴ levator ani syndrome²³ and gastroparesis,²⁴ and in spino-anorectal and afferent anocortical neurophysiology,²⁰ although there is very limited and evolving evidence. Also, 1 Hz stimulation improved vasomotor control and autonomic function,²⁵ suggesting that the aforementioned mechanisms likely mediated the effects of TNT.

Current treatments remain unsatisfactory and at best 25%–50% of patients achieve acceptable continence,^{7,9,26–29} as attested by a recent large multicenter randomized trial where approximately 29% of patients receiving biofeedback therapy or dextranomer injection were primary outcome responders.²⁹ Here, we found that TNT provided a higher therapeutic efficacy. Also, the anal squeeze pressures and sustained squeeze pressures significantly increased in the TNT groups, suggesting that the neurophysiological improvement likely enhanced anal sphincter function. Further, a systematic review of sacral nerve stimulation concluded that 26 of 40 studies showed no changes in anal sphincter function, and 20 of 37 studies showed no changes in rectal sensation, implying that its mechanistic effects are unclear.³⁰ In contrast, as shown here, TNT, by targeting multiple nerves in the lumbosacral plexus likely conferred a multidimensional neuromodulatory beneficial effect on FI pathophysiology.

TNT was well tolerated with very few adverse effects such as paresthesia and back ache. Three patients had serious adverse events unrelated to the treatment. Overall TNT was safe with no differences in adverse events compared with sham. The device tolerability assessment showed no differences between the groups and >75% of patients rated TNT as safe and useful. Also, 80% favored recommending TNT to others.

The limitations of our study include the smaller number of male subjects but this is consistent with other FI

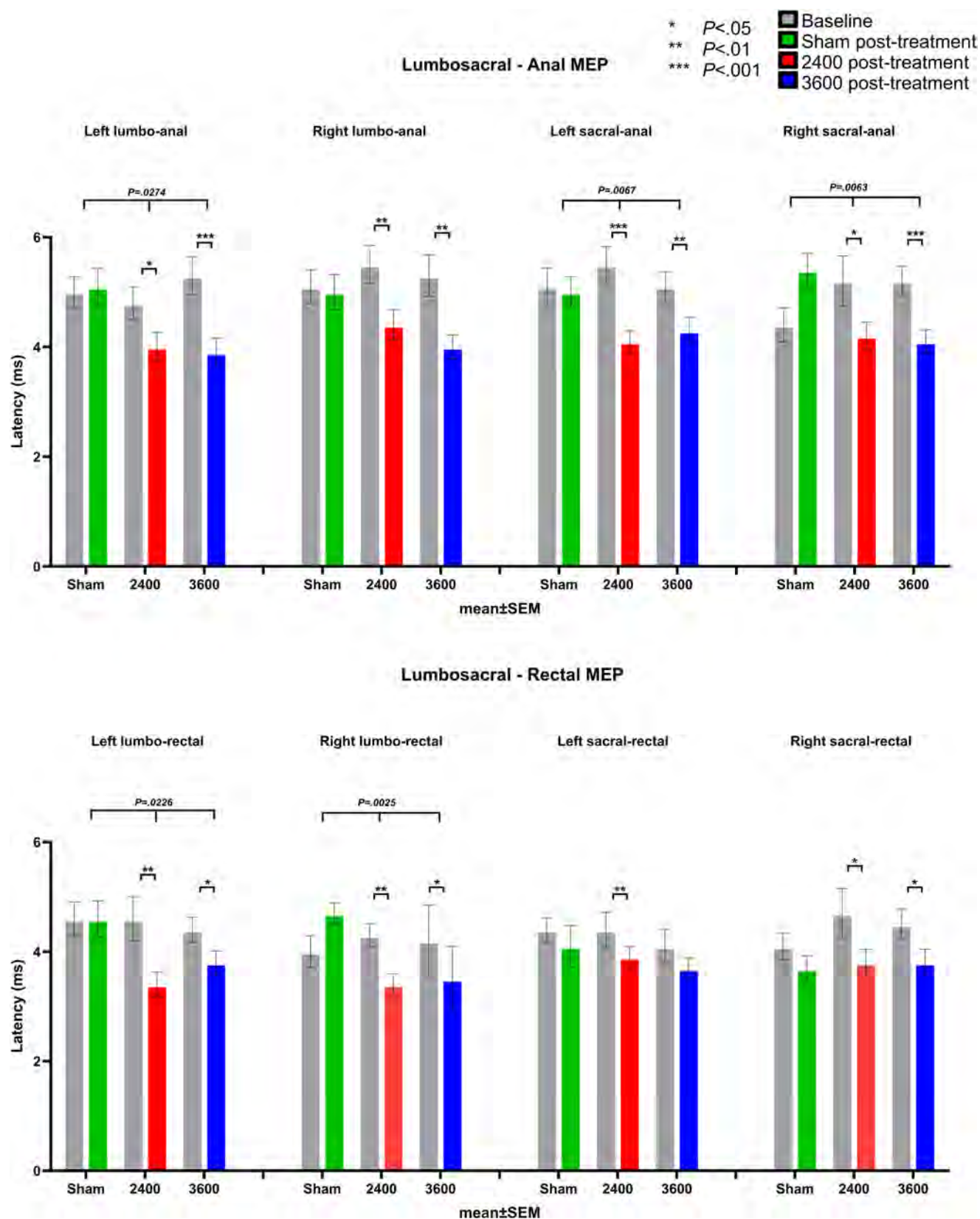


Figure 4. Effects of TNT and sham treatment on anal and rectal neuropathy as assessed using bilateral lumbar and sacral MEP latencies.

Table 3. Adverse Events

Adverse events	Sham	2400	3600
Gastrointestinal			
Acute hepatitis			1 ^a
Rectal bleeding			1
Anal pain		1	
Acute diarrhea			1
Nausea and vomiting	1	2	
Musculoskeletal			
Back pain	2	2	2
Musculoskeletal pain			1
Bone fracture		1	
Numbness and tingling		1	1
Genitourinary			
Urinary urgency		1	1
Urosepsis		1 ^a	
Urinary tract infection			1
Vascular			
Venous thrombosis			2
Infectious			
Upper respiratory tract infection	2	3	3
Neurologic			
Ocular migraine			1
Dizziness		2	
Fall		1 ^a	

^aSerious adverse event.

studies.^{9,26–29} Typically, more women with FI seek health-care due to greater disease burden³¹ despite similar gender prevalence.¹ The sham coil generates a low-frequency magnetic energy and may account for some improvements in the sham group, although most outcomes were significantly better with TNT. The lower baseline frequency of FI in the sham group may cause lesser improvement, but it is unlikely as there was no difference between groups at baseline, and the post-treatment change was 2-fold higher in TNT groups. Although patients and investigators were blinded to the 3 treatment arms, there is room for performance bias as the person administering treatment was not blinded. However, the sham control arm, diary-based outcome assessments, and standardized staff training procedures should have obviated this. The durability of TNT needs assessment in a longer-term, sham-controlled study that is currently underway. Although higher dose of 3600 pulses had more responders than 2400 pulses, this was not significant, a reflection of the study power.

This sham-controlled study met the primary outcome by demonstrating significant improvements in FI episodes in both the TNT groups when compared with sham group. TNT, a novel, noninvasive, outpatient-based treatment, was safe, well tolerated, and efficacious in improving FI symptoms, its severity, and lumbosacral neuropathy in patients with moderately severe FI.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <https://doi.org/10.1053/j.gastro.2026.04.027>.

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CRedit Authorship Contributions

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 Shaheen Hamdy, FRCP (Consultant, manuscript preparation, critical revisions: Equal)
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Conflicts of interest

This author discloses the following: Dr Satish S.C. Rao holds a patent for trans-lumbosacral neuromodulation therapy, No. 11484726. The remaining authors disclose no conflicts.

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Data Availability

All authors reviewed and approved the final version of the manuscript. Satish S.C. Rao, MD, PhD, takes responsibility for the integrity of the work from inception to publication, and can be contacted to request access to some of the available data.

Portions of this work were presented at Digestive Diseases Week, 2025, and published as an abstract: Yan Y, et al. *Gastroenterology* 2025;169:S-149–S-150.

Supplemental information

Randomized Sham-Controlled Trial of Translumbosacral Neuromodulation Therapy for Fecal Incontinence

Satish S.C. Rao, Yun Yan, Shaheen Hamdy, Kyle Staller, Karlo Fidel, Abeer Aziz, Amol Sharma, Jenna Clukey, Deepak Ayyala, and Braden Kuo

Supplemental Figure Legends

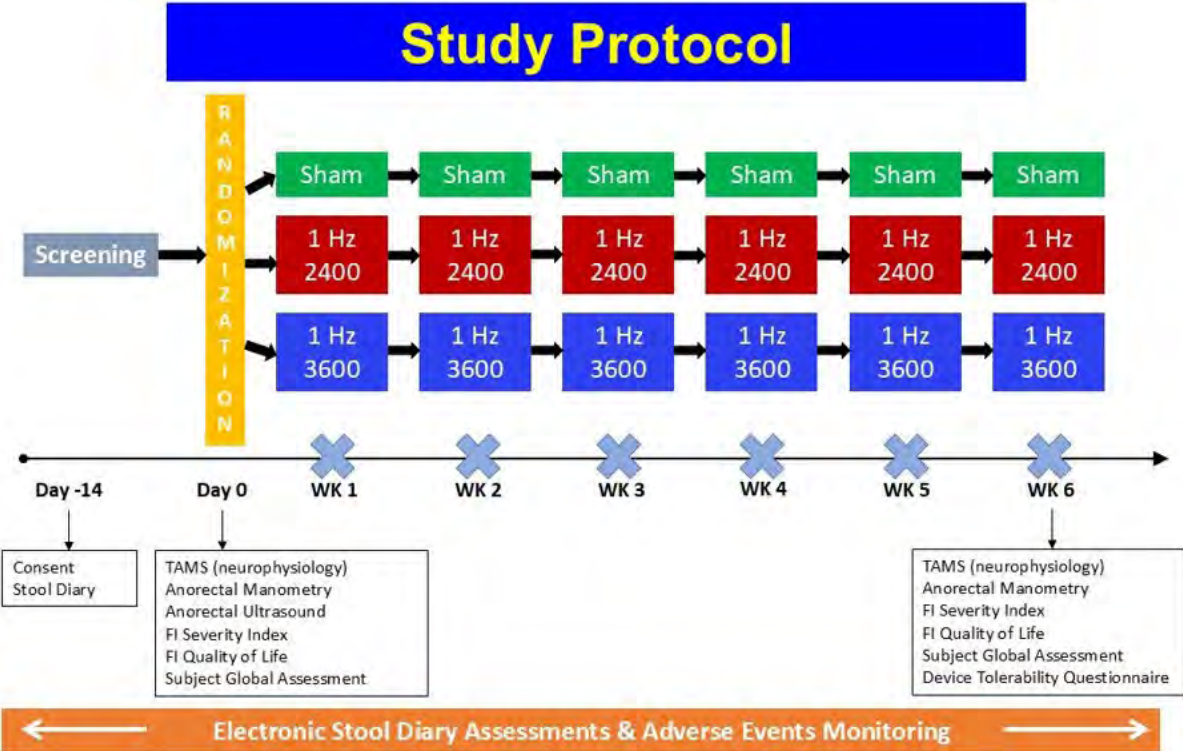
Supplementary Figure 1. Study Protocol

Supplementary Figure 2. This shows the methodology used for administering the TNT therapy.

Here, a patient is seen lying in the prone position with an air-cooled magnetic coil (A) device that is located over the lumbar region on the left side with a coil fixator device (B). Also seen is the magnetic energy generator (C) which is attached to the coil.

Supplementary Figure 3. Device and Treatment Tolerability Questionnaire responses as assessed under 3 domains in the TNT and sham groups after treatment.

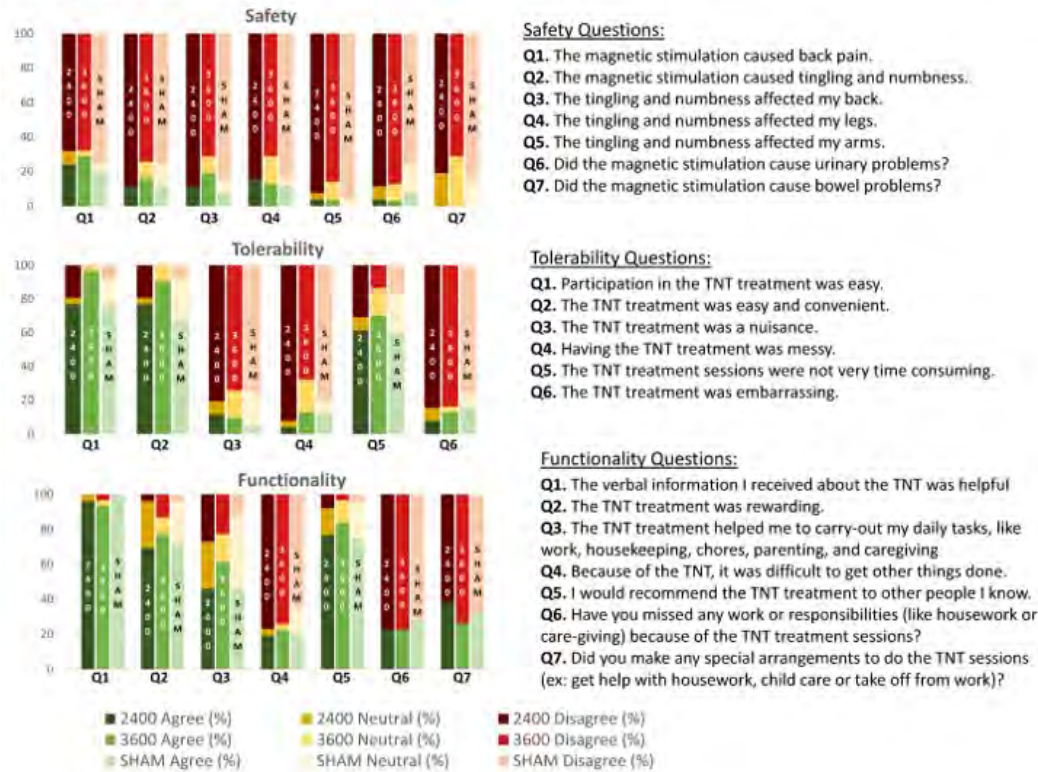
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Supplemental Figure 3. Device and Treatment Tolerability Questionnaire responses as assessed under 3 domains in the TNT and sham groups after treatment.



Supplementary Table 1. Comparison of Lumbosacral plexus motor-evoked potential latencies at the anal and rectal sites between historical healthy controls⁵ and FI patients participating in the TNT trial (mean (95%CI))

Site	Healthy Controls (n=31)	Sham (n=34)		2400 (n=38)		3600 (n=37)	
		Baseline	p-value	Baseline	p-value	Baseline	p-value
Anal, <u>ms</u>							
Left Lumbar	3.38 (3.1-3.6)	5.01 (4.4-5.5)	<0.001	4.80 (4.2-5.3)	<0.001	5.28 (3.9-4.8)	<0.001
Left Sacral	2.99 (2.7-3.2)	5.05 (4.3-5.7)	<0.001	5.48 (4.8-6.1)	<0.001	5.16 (4.6-5.7)	<0.001
Right Lumbar	3.39 (3.1-3.6)	5.14 (4.4-5.7)	<0.001	5.48 (4.7-6.1)	<0.001	5.28 (4.5-6.0)	<0.001
Right Sacral	3.14 (2.9-3.4)	4.48 (3.8-5.1)	<0.001	5.24 (4.3-6.1)	<0.001	5.19 (4.6-5.7)	<0.001
Rectal, <u>ms</u>							
Left Lumbar	2.89 (2.7-3.1)	4.56 (3.9-5.1)	<0.001	4.61 (3.8-5.4)	<0.001	4.41 (3.9-4.8)	<0.001
Left Sacral	2.92 (2.6-3.2)	4.39 (3.7-4.9)	<0.001	4.4 (3.9-4.8)	<0.001	4.13 (3.7-4.5)	<0.001
Right Lumbar	3.17 (2.9-3.4)	4.01 (3.5-4.4)	<0.001	4.31 (3.6-4.9)	<0.001	4.2 (3.5-4.8)	<0.001
Right Sacral	2.97 (2.7-3.3)	4.06 (3.5-4.5)	<0.001	4.71 (3.7-5.6)	<0.001	4.47 (3.8-5.0)	<0.001

p-values are compared to historical healthy controls

Supplementary Table 2: Effects of TNT and sham treatment on anal sphincter function. (Mean (95% CI)).

	Sham (N=34)			2400 (N=38)			3600 (N=37)			P#
	Baseline	Post-treatment	p-value	Baseline	Post-treatment	p-value	Baseline	Post-treatment	p-value	
Resting Pressure (mmHg)	52.5 (45.0-60.0)	56.3 (48.3-64.1)	0.23	57.8 (47.4-68.1)	59.4 (51.5-67.1)	0.70	56.7 (48.8-64.5)	62.1 (53.8-70.3)	0.06	0.73
Maximal Squeeze Pressure (mmHg)	135.0 (111.0-158.8)	134.9 (111.7-157.9)	0.99	127.7 (112.3-142.9)	161.8 (141.2-182.4)	<0.001	133.0 (110.0-155.8)	148.1 (121.3-174.9)	0.04	0.005
Sustained Squeeze Pressure (mmHg)	60.8 (49.7-71.8)	70.1 (59.7-80.4)	0.06	65.4 (58.0-72.6)	88.7 (80.1-97.1)	<0.001	75.6 (61.0-90.2)	89.2 (74.6-103.7)	<0.001	0.04

P# Overall Difference among groups