Published in final edited form as:

Am J Gastroenterol. 2020 January ; 115(1): 115–127. doi:10.14309/ajg.0000000000000482.

Characteristics Associated With Clinically Important Treatment Responses in Women Undergoing Non-Surgical Therapy for Fecal Incontinence

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Specific role of each author: All authors were involved in the planning and/or conducting of the secondary analysis, collecting and/or interpreting data, drafting and approval of the final manuscript.

Guarantor of article: Ms. Iyer and Dr. Gantz from the data coordinating center (RTI) accept full responsibility for the data analysis.

COI/financial disclosures:

Richter: Grant support: Pelvalon, Renovia, Allergan, NICHD, PCORI, NIA

Jelovsek: None

Iyer: None

Rogers: None

Meyer: None

Newman: Consulting and grant support GTx Inc, NIH NIDDK grant support

Bradley: None

Harm-Ernandes: None

Dyer: Pelvalon, Inc, grant support

Wohlrab: None

Mazloomdoost: None

Gantz: On behalf of the Pelvic Floor Disorders Network, diagnostic and treatment equipment for the primary trial was provided by Medspira, Inc at a discounted rate for consultation with network investigators on the development of biofeedback software.

Potential Competing Interests: None

Abstract

Objective: To identify baseline clinical and demographic characteristics associated with clinically important treatment responses in a randomized trial of non-surgical therapies for fecal incontinence (FI).

Methods: Women (N=296) with FI were randomized to loperamide or placebo and manometry-assisted biofeedback exercises or educational pamphlet in a 2×2 factorial design. Treatment response was defined in 3 ways: minimally clinically important difference (MID) of −5 points in St. Mark's score, 50% reduction in FI episodes and combined St. Mark's MID and 50% reduction FI episodes, from baseline to 24 weeks. Multivariable logistic regression models included baseline characteristics and treatment group with and without controlling for drug and exercise adherence.

Results: Treatment response defined by St. Mark's MID was associated with higher symptom severity (adjusted Odds Ratio [aOR] 1.20, 95%CI 1.11 – 1.28) and being overweight vs normal/underweight (aOR 2.15, 95%CI 1.07 – 4.34); these predictors remained controlling for adherence. 50% reduction in FI episodes was associated with combined loperamide/biofeedback group compared to placebo/pamphlet (aOR 4.04, 95%CI 1.36 – 11.98), St. Mark's score in the placebo/pamphlet group (aOR 1.29, 95%CI 1.01–1.65), FI subtype of urge vs urge plus passive FI (aOR 2.39, 95%CI 1.09–5.25) and passive vs urge plus passive FI, (aOR 3.26, 95% CI 1.48–7.17). Controlling for adherence, associations remained, except St. Mark's score.

Conclusion: Higher severity of FI symptoms, being overweight, drug adherence, FI subtype, and combined biofeedback and medication treatment were associated with clinically important treatment responses. This information may assist in counseling patients regarding efficacy and expectations of non-surgical treatments of FI.

Keywords

fecal incontinence; anal incontinence; biofeedback; anorectal manometry; loperamide

Introduction

Fecal incontinence (FI), also referred to as accidental bowel leakage, is a condition which significantly impacts quality of life with prevalence ranging from 2 to 21%.¹ To optimize treatment outcomes it is important to understand demographic and clinical factors associated with treatment success. Primary treatment strategies for FI include dietary modifications, pharmacotherapy and anorectal exercises with or without biofeedback.² A commonly used medication for FI is loperamide (Imodium™), a synthetic opioid that has been shown to be more effective than placebo at controlling FI episodes.³ Additionally, anorectal manometry (ARM)-assisted biofeedback can enhance muscle contraction, coordination, and rectal sensation with improvements in FI symptoms, but consensus on timing and length of intervention does not exist.^{4,5} Unfortunately, no single treatment for FI provides consistent, long-term effectiveness and low complication rates.⁶

This was a planned secondary analysis of a large trial (Controlling Anal incontinence by Performing Anal Exercises with Biofeedback or Loperamide, CAPABLE) where women

with FI were randomized to non-surgical therapies of loperamide vs placebo and ARM-assisted biofeedback exercises vs educational pamphlet in a 2×2 factorial design.⁷ The objective of this report was to evaluate whether clinical and demographic characteristics serve as modifiers of the CAPABLE treatment effects, and to identify baseline characteristics associated with clinically important treatment responses to non-surgical fecal incontinence therapies in women 24 weeks after treatment.

Methods

This was a secondary analysis of the Controlling Anal incontinence by Performing Anal Exercises with Biofeedback or Loperamide (CAPABLE) randomized trial ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02008565); NCT02008565). Women were randomized in a 2×2 factorial design using a 0.5:1:1:1 allocation to one of four groups: 1) oral placebo plus education only, 2) placebo and ARM-assisted biofeedback exercises, 3) loperamide plus education only and 4) loperamide and ARM-assisted biofeedback exercises, respectively. Education consisted of a publicly available pamphlet from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with deletion of a single reference to the drug loperamide. The pamphlet, which discusses symptoms, causes, diagnosis, as well as dietary management for bowel control problems was provided to all CAPABLE participants.

The study design has been previously published.⁷ Women over 18 years of age with bothersome, at least monthly FI over the preceding 3 months and negative colon cancer screening were eligible to participate. Women who reported Type 1 (hard) or Type 7 (watery) stool consistency over the last 3 months using the Bristol Stool Form were excluded.⁸ All sites received Institutional Review Board (IRB) approval and all participants provided written informed consent.

Baseline demographic and clinical variables included age, race, ethnicity, insurance type, body mass index, obstetric history, menopausal status, estrogen use, smoking status, connective tissue disease, pelvic surgical history, Bristol stool index, Rome III irritable bowel syndrome (IBS) status, and a 7-day bowel diary that measured leakage types, episodes, and pad use. Obstetric history was described as those who underwent any or no vaginal births, and any or no Cesarean deliveries.

Symptoms of fecal incontinence were measured using validated questionnaires including St. Mark's (Vaizey) Questionnaire,^{9,10} Colorectal-Anal subscales of the Pelvic Floor Distress Inventory (CRADI) Short Form,¹¹ Colorectal-Anal subscale of the Pelvic Floor Impact Questionnaire (CRAIQ)¹¹ and the Modified Manchester Health Questionnaire (MMHQ) severity subscale.¹² Other clinical variables measured included anal manometry measures as described in the design paper,⁷ anal sphincter tone,¹³ dietary fiber intake¹⁴ and a provider-reported adherence question.¹⁵ Treatment adherence was defined based on response to a single provider-reported question, "When was the last time this patient missed any of her medication for bowel leakage?" or "When was the last time the patient missed any of the exercises for bowel leakage?". Questionnaires and bowel diaries were completed at baseline and at 24 weeks follow-up.

Clinically important treatment response was defined in three ways using validated measures: 1) as a minimal clinically important difference (MID) of -5 points in St. Mark's score⁹ and 2) as a 50% reduction in FI episodes and 3) combined St. Mark's MID and 50% reduction in FI episodes, from baseline to 24 weeks.^{16,17,18} Bivariate comparisons of baseline characteristics between responders and non-responders were conducted using t-tests, chi-square tests, or Fisher's exact tests. Multivariable logistic regression models were constructed to predict responder status based on assigned treatment group and baseline characteristics. Covariates were selected based on clinical interpretability, presence in >10% of participants (for categorical variables), and statistical significance between response groups at $p < 0.2$ on bivariate analysis. To evaluate whether covariates were modifiers of the CAPABLE treatments, interactions with treatment were evaluated for one covariate at a time, and the final model included interactions that were significant at $p < 0.05$. In addition, adherence to drug and exercise interventions were evaluated as predictors of treatment response by including those variables in a second version of the final models. Due to low numbers, adherence response categories of "last missed" treatment in the past 1–2 weeks and 2–4 weeks were combined, and categories of 1–3 months and >3 months were combined for modeling purposes. Because adherence to exercise was not assessed in participants not randomized to ARM-assisted biofeedback, those participants were classified as having "never missed" their assigned intervention. Adjusted odds ratios (aOR) are presented with 95% confidence intervals (CI).

Results

Participants

Overall baseline participant characteristics are displayed in Table 1; mean age ($\pm$ standard deviation) was 63.7 ± 11.1 years, 79% were White, mean BMI was 29.9 ± 7.5 kg/m² and 85% were postmenopausal. Of 296 eligible participants randomized in the primary trial the number of participants missing outcome data post-randomization at 24 weeks was similar among groups.¹⁹ In this current analysis, 266 (90%) women had primary outcome data available using the St. Marks score and 256 (87%) had bowel diary data available at 24 weeks.

Treatment Response by St Mark's Score MID Achievement

Of the 266 subjects with outcome data, 137 (52%) and 129 (48%) patients were classified as responders and non-responders, respectively, using the MID of 5-point or greater improvement in the St. Marks score at 24 weeks (Table 2). Baseline differences between responders and non-responders included body mass index (BMI) by category, vaginal estrogen therapy use, treatment group, FI severity, anal sphincter tone. Treatment adherence at 24 weeks reflected a greater proportion of responders having "never missed" their exercises (32% responders vs. 16% non-responders, $p=0.01$) and medications (52% responders vs. 35% non-responders, $p=0.03$).

Multivariable analyses (Table 3a) revealed that treatment response was independently associated with higher baseline St. Mark's score (aOR 1.20, 95%CI 1.11 – 1.28) and being overweight vs normal/underweight (adjusted OR [aOR] 2.15, 95%CI 1.07 – 4.34). In the

model controlling for adherence (Table 3b), these predictors remained with additional variable of drug adherence, specifically, missed within the past week vs never missed (aOR 0.35, 95%CI 0.16–0.78) or missed in the past 1–4 weeks vs never missed (aOR 0.37, 95%CI 0.15–0.88).

Treatment Response by 50% FI Episode Reduction

Of 256 subjects with bowel diaries at 24 weeks, 174 (68%) and 82 (32%) subjects were classified as responders versus non-responders, respectively, defined as 50% FI episode reduction. Characteristics associated with differences between responders and non-responders included (Table 4) randomized treatment group, prior rectal or anal surgery, mean fecal incontinence episodes/week, FI type, mean St. Mark's scores, and mean MMHQ score. Treatment adherence at 24 weeks did not differ between groups for adherence to exercise ($p=0.53$) or adherence to drug ($p=0.86$).

Multivariable analysis (Table 5a) revealed that baseline St. Mark's score was a modifier of assigned treatment. At a baseline St. Mark's score of 14.2 (the average among participants in the model), women in the combined loperamide/biofeedback group were more likely to achieve a 50% reduction in FI episodes compared to control (placebo/educational pamphlet), aOR 4.04, 95%CI 1.36 – 11.98. Baseline St. Mark's score was a predictor of response among women assigned to placebo and education only (aOR 1.29, 95%CI 1.01–1.65). Additionally, FI subtypes of urge vs urge plus passive FI (aOR 2.39, 95%CI 1.09–5.25) and passive vs urge plus passive FI, (aOR 3.26, 95% CI 1.48–7.17) were independently associated with achieving a 50% reduction in FI episodes. Controlling for adherence, associations remained, except St. Mark's score (Table 5b).

Treatment Response by both St. Mark's Score MID and 50% FI Episode Reduction

There were 108/262 (41%) participants who were responders meeting both the St. Mark's MID and 50% reduction in FI episode definitions. Response according to both criteria was independently associated with urge vs urge plus passive FI (aOR 2.40, 95%CI 1.11 – 5.19), passive vs urge plus passive FI (aOR 2.64, 95%CI 1.26 – 5.52), higher anal sphincter tone squeeze score (aOR 1.29, 95%CI 1.00 – 1.66), and higher baseline St. Mark's score (aOR 1.19, 95%CI 1.11 – 1.28) [Supplemental Tables]. Although randomized treatment group was a significant predictor overall, comparisons between individual active treatment groups vs. control were not significant. Controlling for adherence, treatment response was associated with passive FI, St. Mark's score, and drug adherence of missed within the past week vs never missed (aOR 0.37, 95%CI 0.17–0.84) or missed in the past 1–4 weeks vs never missed (aOR 0.37, 95%CI 0.15–0.94).

Discussion

Among women with at least monthly FI over three months prior to trial participation, those with higher baseline severity, adherence to drug therapy, and who were overweight were more likely to meet the criteria for treatment response as measured by the MID of the St. Mark's scale, a validated subjective outcome measure. A 50% reduction in FI episodes as measured by bowel diary, another validated objective measure, was associated with higher

baseline FI symptom severity, FI type, and randomization assignment to combined therapy. Despite the index randomized trial showing no differences in the primary outcome of difference from baseline to 24 weeks in St. Mark's (Vaizey) FI score,¹⁹ this secondary analysis demonstrated that treatment assignment and specific clinical and demographic characteristics were independently associated with 2 recognized definitions of clinical treatment response. The primary trial looked at overall change in St. Mark's score from baseline to 24 weeks in women undergoing 1 of 4 treatment allocations. This secondary analysis looked at predictors associated with clinically significant changes in the 2 outcomes measures.

Results of studies investigating the relationship between symptom severity and treatment response are mixed. A large retrospective study (N=513) characterized predictors of successful biofeedback treatment as completion of all treatment sessions (adherence), female gender, older age and more severe symptoms (OR 1.2 per unit increase in St. Mark's score, 95% CI 1.05–1.34), consistent with the current study's findings.⁴ Other studies found higher FI severity scores were associated with worse outcomes from biofeedback or pelvic floor therapy treatment.^{20,21,22} However, these studies had lower numbers,^{20,21} shorter-term response time-point,²⁰ used different severity measures²⁰ and overall mean treatment responses did not meet the MID.²² In the current trial, the mean number of FI episodes per week at baseline was 11 and the mean Vaizey score was 14 out of a potential maximum score of 24, characterizing a severely affected population. It may be that having a higher severity allows a greater chance to meet an MID for symptom improvement. The current results would suggest that women with greater symptom severity do have higher potential to achieve clinically important improvement with these treatments than women with lower burden of disease.

Treatment adherence with loperamide, and combined therapy of loperamide and ARM-assisted biofeedback exercises were associated with achieving an MID in treatment outcome. Others have found that treatment success was associated with completion of all treatment sessions (reflecting adherence).⁴ A secondary analysis of another randomized trial compared outcomes of rectal balloon training plus pelvic floor muscle training versus pelvic floor muscle training alone (N=80). The addition of a constipating medication (combined active therapy) was associated with increased odds of a favorable outcome.²³ Intuitively, it makes sense that adherence to effective treatment may result in achieving clinically important differences.

Increased BMI is a known risk factor for FI^{24,25} and others have reported that with each unit increase of BMI, the odds of FI increased by 6%.²⁶ In the current study we found that overall BMI (viewed continuously) was not associated with achieving the St. Mark's MID, however one subtype, being overweight vs normal/underweight, was associated with treatment response. While it is unclear why being overweight was associated with treatment success, it is possible that factors that may impact treatment response are inherently different from those that predict presence of disease. For example, one study looking at the effect of weight loss in overweight and obese women on FI symptoms found that those with anal incontinence were 2.5 times more likely to have a lower fiber intake.²⁷

Fecal incontinence subtype was also noted to be a predictor of treatment response where having either passive or urge associated FI compared to both incontinence types was associated with symptom improvement. Little data exist regarding the impact of FI incontinence type on clinically important treatment response. In one large study looking at predictors of outcome in 258 patients undergoing pelvic floor rehabilitation for FI, passive FI was noted to be associated with a worse outcome.²² In a meta-analysis of sacral nerve stimulation, the ability to defer defecation (with an urge to go) was associated with improved symptoms among women with an impaired anal sphincter.²⁸

The only variable associated with achieving both treatment response criteria was higher anal sphincter tone squeeze score as determined on physical examination. Maximum squeeze pressure has been found to be a predictor of positive outcome for biofeedback plus anal electrostimulation²⁹ and pelvic floor rehabilitation,²² however those sphincter pressures were obtained with anal manometry. It is clinically plausible that higher anal squeeze pressure may contribute to achieving combined objective and subjective treatment responses.

It is not surprising that some variables varied between the two definitions of treatment response or that a higher proportion of participants (68% vs 52%) achieved treatment response with an objective response definition. Subjective quality of life measures such as the St. Mark's questionnaire may reflect different patient experiences compared to a more objective measure of FI episode reduction. Previously, predictors of outcome concentrated on objective measures, such as manometric parameters and sonographic findings, however, these measures have limited reproducibility.^{20,22,23} Consistent with these findings, no diagnostic testing measures, other than a physical examination, digital assessment of anal sphincter squeeze, were noted to be associated with either measure of treatment response.

The main strength of this study is that it was a planned secondary analysis of a large randomized controlled clinical trial with a well-characterized study population and low loss to follow-up.¹⁹ Subjective assessment of symptoms was performed using validated instruments and objective evaluation of FI episodes using bowel diaries were administered at baseline and 24 weeks follow-up. Definitions of treatment response were those consistently reported in the literature and are validated. A Cochrane review of FI treatments called for the use of validated subjective measures and analyses based on clinically important differences.³ Mean number of FI episodes at baseline was 11 per week providing a significantly impacted population to characterize variables associated with treatment response. Treatment interventions were standardized across sites with centrally trained and certified practitioners performing the biofeedback.³⁰ Finally, a broad inclusion of potential characteristics was provided which is important, especially given the lack of an understanding of well-defined predictors for FI treatment response.²³

The majority of the current study population was white and menopausal, which limits the generalizability to other populations. Significant differences in adherence were noted between responder and non-responders defined by the St. Mark's MID; however, even after controlling for adherence, symptom severity and being overweight were associated with treatment response. This finding may improve the overall generalizability of these results

since patient adherence is known to be an issue with pharmacotherapy as well as with biofeedback.

With increased focus on patient centered outcomes and unreliable correlation between diagnostic testing measures and symptom severity, degree of bother and response to treatment, there should be greater focus on predictors that can be readily obtained at an office visit. Assessment of these clinical and demographic characteristics and validated questionnaires do not require patients to undergo invasive testing. Especially when evaluating non-surgical therapies, higher cost and discomfort associated with invasive testing may not be warranted. This information will allow providers to more specifically counsel patients that even women with severe FI symptoms may benefit from non-surgical therapy, help provide expectations of treatment and discuss strategies for patients to optimize outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Brown University: B. Star Hampton, Cassandra Carberry, Charles R. Rardin, Deborah L. Myers, Vivian W. Sung; Cleveland Clinic Foundation: Annette Graham, Marie Fidela R. Paraiso, Beri Ridgeway; Duke University: Cindy Amundsen, Amy Pannullo, Anthony Visco, Nazema Siddiqui, Shantae McLean; Kaiser San Diego: Gouri Diwadkar, Keisha Dyer; RTI: Amanda Shaffer, Benjamin Carper, Brenda Hair, Carla M. Bann, Kristin Zaterka-Baxter, Lauren Klein Warren, Lynda Tatum, Ryan E. Whitworth, Tamara L. Terry, Yan Tang; University of Alabama at Birmingham: Alicia Ballard, Alayne Markland, Jeannine McCormick, Kathy Carter; University of California, San Diego: Charles Nager; University of New Mexico: Christy Miller, Erin Yane, Gena Dunivan, Julia Middendorf, Peter Jeppson, Sara Cichowski, Yuko Komesu; University of Pennsylvania: Ariana Smith, Heidi Harvie, Lily Arya, Uduak Umoh Andy; University of Pittsburgh: Halina M. Zyczynski, Judy Gruss, Pam Moalli

Funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institutes of Health Office of Research on Women's Health; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01502956) number, [NCT01502956](https://clinicaltrials.gov/ct2/show/study/NCT01502956). The design, collection, analysis, interpretation of data was performed by the clinical sites of the Pelvic Floor Disorders Network with RTI International, the data coordinating center.

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STUDY HIGHLIGHTS:**1. WHAT IS KNOWN**

- Fecal incontinence significantly impacts quality of life.
- Primary treatment approaches for fecal incontinence are non-surgical including dietary management, pharmacologic and anal muscle exercises.
- It is unclear what baseline patient characteristics are associated with a clinically important treatment response to non-surgical treatments.

2. WHAT IS NEW HERE

- Patient characteristics associated with a clinically important treatment response to non-surgical fecal incontinence treatment were identified.
- Women with higher symptom severity had clinically important improvement with non-surgical treatment.
- Women in the combined anorectal manometry-assisted biofeedback exercises and active pharmacotherapy group were more likely to meet criteria for a clinically important treatment response.
- Baseline anorectal manometry measures were not associated with a clinically important treatment response to non-surgical therapy.

Table 1:

Baseline Clinical, Demographic and Adherence Characteristics of All CAPABLE Participants

Characteristics	N=296
Age, Mean (SD)	63.7 (11)
Race, N (%)	
White	234 (79)
Black/African American	46 (16)
American Indian/Alaskan Native	3 (1)
More than one race	5 (2)
Other	8 (3)
Ethnicity, N (%)	
Hispanic/Latina	26 (9)
Not Hispanic/Not Latina	265 (90)
Unknown/Not Reported	5 (2)
BMI, kg/m ²	
Mean (SD)	29.9 (7.5)
Median (min—max)	28.4 (17—68)
BMI (categorized) N, (%)	
Normal/Underweight (< 25)	81 (28)
Overweight (25 – 29)	91 (31)
Obese (≥ 30)	123 (42)
Type of Insurance, N (%)	
Medicaid/Medicare	158 (53)
Self-Pay	4 (1)
Private/HMO	181 (61)
Other	22 (7)
Vaginal Deliveries (categorized), N (%)	
Had prior vaginal delivery	259 (88)
Median (min-max)	2 (0 – 7)
Cesarean Deliveries	
Had prior cesarean delivery, N (%)	35 (12)
Median (min-max)	0 (0 – 5)
Menstrual Status, N (%)	
Pre-Menopausal	29 (10)
Post-Menopausal	251 (85)
Not sure	16 (5)
Estrogen Therapy - Vaginal, N (%)	75 (25)
Estrogen Therapy - Oral Patch, N (%)	28 (10)
Current Smoker Status, N (%)	21 (7)
Connective Tissue Disease Status, N (%)	12 (4)

Characteristics	N=296
Randomized Treatment, N (%)	
Loperamide with Biofeedback	85 (29)
Loperamide with Education Only	86 (29)
Placebo with Biofeedback	83 (28)
Placebo with Education Only	42 (14)
Prior pelvic surgery history, N (%)	
Prior Accidental Bowel Leakage Surgery	13 (4)
Prior Rectal or Anal Surgery	40 (14)
Prior Hysterectomy	148 (50)
Prior Urinary Incontinence Surgery	77 (26)
Prior Pelvic Organ Prolapse Surgery	70 (24)
Bristol Stool Index, N (%)	
Type 1 - Separate hard lumps like nuts	0 (0)
Type 2 - Sausage shaped but lumpy	45 (15)
Type 3 - Like a sausage but with cracks on its surface	43 (15)
Type 4 - Like a sausage or snake, smooth and soft	93 (31)
Type 5 - Soft blobs with clear cut edges	53 (18)
Type 6 - Fluffy pieces with ragged edges, a mushy stool	62 (21)
Type 7 - Watery, no solid pieces	0 (0)
Average Total Number of Leaks/Week	
Mean (SD)	11.1 (12.5)
Median (min—max)	7 (0—80)
Fecal Incontinence Type, N (%)	
Urgency	99 (33)
Passive	125 (42)
Both	72 (24)
Maximum Anal Canal Pressure, Resting (mm/Hg)	
Mean (SD)	41.0 (18.8)
Maximum Anal Canal Pressure, Squeeze (mm/Hg)	
Mean (SD)	73.0 (33.2)
Anal Sphincter Tone, Squeeze Score	
Mean (SD)	1.8 (1.1)
¹ St. Mark's Score	
Mean (SD)	14.2 (4.1)
² CRADI Score	
Mean (SD)	50.4 (22.0)
³ CRAIQ Score	
Mean (SD)	43.4 (28.3)

Characteristics	N=296
⁴ MMHQ Severity Measures Score	
Mean (SD)	56.1 (24.5)
Exercise Adherence (last time exercise was missed) - 24 weeks, N (%)	
Within the past week	78 (50)
1–2 weeks	15 (10)
2–4 weeks	5 (3)
1–3 months	12 (8)
> 3 months	7 (5)
Never missed	39 (25)
Drug Adherence (last time drug was missed)- 24 weeks, N (%)	
Within the past week	53 (21)
1–2 weeks	23 (9)
2–4 weeks	15 (6)
1–3 months	33 (13)
> 3 months	20 (8)
Never missed	111 (44)

SD, standard deviation

¹ St. Mark's (Vaizey) Questionnaire [range (least impact) 0–24 (most impact), minimum important difference –5]^{9,10}

² Colorectal-Anal subscales of the Pelvic Floor Distress Inventory Short Form [CRADI, range 0 (least impact) –100 (most impact)]¹¹

³ Colorectal-Anal subscale of the Pelvic Floor Impact Questionnaire [CRAIQ, range 0 (least impact) –100 (most impact)]¹¹

⁴ Modified Manchester Health Questionnaire severity subscale [MMHQ, range 0 (least impact) –100 (most impact)]¹²

Table 2:

Baseline Clinical, Demographic and Adherence Characteristics by St. Mark's MID Treatment Response

Measurements	Responders N=137	Non-Responders N=129	p-value
Age			0.99
Mean (SD)	63.8 (10.7)	63.8 (11.4)	
BMI kg/m ²			0.37
Mean (SD)	30.2 (6.9)	29.4 (7.1)	
Median (min—max)	28.4 (17—55)	28.5 (17—62)	
BMI (categorized), N (%)			0.046
Normal/Underweight (< 25)	29 (21)	43 (33)	
Overweight (25 – 29)	50 (37)	33 (26)	
Obese (≥ 30)	57 (42)	53 (41)	
Vaginal Deliveries, N (%)			0.94
Median (min-max)	2 (0 – 7)	2 (0 – 7)	
Vaginal Deliveries (categorized), N (%)			0.58
Yes	122 (89)	112 (87)	
Cesarean Deliveries			0.04
Median (min-max)	0 (0 – 3)	0 (0 – 4)	
Cesarean Deliveries (categorized), N (%)			0.01
Yes	8 (6)	20 (16)	
Menstrual Status, N (%)			0.80
Pre-Menopausal	13 (10)	12 (9)	
Post-Menopausal	118 (86)	109 (85)	
Not sure	6 (4)	8 (6)	
Estrogen Therapy - Vaginal, N (%)			0.16
Yes	30 (22)	38 (30)	
Estrogen Therapy - Oral Patch, N (%)			0.32
Yes	11 (8)	15 (12)	
Current Smoker Status, N (%)			0.71
Yes	9 (7)	10 (8)	
Connective Tissue Disease Status, N (%)			0.62
Yes	7 (5)	5 (4)	
Randomized Treatment, N(%)			0.09
Loperamide with Biofeedback	48 (35)	27 (21)	
Loperamide with Education Only	38 (28)	42 (33)	
Placebo with Biofeedback	34 (25)	40 (31)	
Placebo with Education Only	17 (12.4)	20 (15.5)	
Surgery Type, N (%)			
Prior Accidental Bowel Leakage Surgery	5 (4)	8 (6.2)	0.33
Prior Rectal or Anal Surgery	20 (15)	16 (13)	0.59

Measurements	Responders N=137	Non-Responders N=129	p-value
Prior Hysterectomy	65 (47)	65 (50)	0.63
Prior Urinary Incontinence Surgery	33 (24)	37 (29)	0.40
Prior Pelvic Organ Prolapse Surgery	35 (26)	31 (24)	0.77
Bristol Stool Index, N (%)			0.95
Type 1 - Separate hard lumps like nuts	0 (0)	0 (0)	
Type 2 - Sausage shaped but lumpy	20 (15)	15 (12)	
Type 3 - Like a sausage but with cracks on its surface	21 (15)	18 (14)	
Type 4 - Like a sausage or snake, smooth and soft	44 (32)	45 (35)	
Type 5 - Soft blobs with clear cut edges	24 (18)	24 (19)	
Type 6 - Fluffy pieces with ragged edges, a mushy stool	28 (20)	27 (21)	
Type 7 - Watery, no solid pieces	0 (0)	0 (0)	
Average Total Number of Leaks/Week			0.90
Mean (SD)	10.8 (12.3)	11.0 (12.3)	
Fecal Incontinence Type, N (%)			0.48
Urgency	44 (32)	46 (36)	
Passive	62 (45)	49 (38)	
Both	31 (23)	34 (26)	
Maximum Anal Canal Pressure, Resting (mm/Hg)			0.50
Mean (SD)	40.0 (17.7)	41.5 (19.3)	
Maximum Anal Canal Pressure, Squeeze (mm/Hg)			0.51
Mean (SD)	74.0 (34.4)	71.3 (32.2)	
Anal Sphincter Tone, Squeeze Score			0.17
Mean (SD)	1.9 (1.1)	1.8 (1.1)	
St. Mark's Score			<0.01
Mean (SD)	15.4 (3.6)	12.9 (4.2)	
CRADI Score			0.51
Mean (SD)	49.2 (20.9)	50.9 (22.3)	
CRAIQ Score			0.42
Mean (SD)	40.6 (27.2)	43.4 (28.9)	
MMHQ Severity Measures Score			0.89
Mean (SD)	55.6 (25)	55.1 (23.3)	
Exercise Adherence (last time exercise was missed) - 24 weeks, N (%)			<0.01
the past week	35 (39)	43 (64)	
1-2 weeks	9 (10)	6 (9)	
2-4 weeks	2 (2)	3 (5)	
1-3 months	11 (12)	1 (2)	
> 3 months	4 (5)	3 (5)	
Never missed	28 (32)	11 (16)	
Drug Adherence (last time drug was missed) - 24 weeks, N (%)			0.03

Measurements	Responders N=137	Non-Responders N=129	p-value
Within the past week	20 (15)	33 (27)	
1–2 weeks	10 (8)	13 (11)	
2–4 weeks	5 (4)	10 (8)	
1–3 months	20 (15)	13 (11)	
> 3 months	9 (7)	11 (9)	
Never missed	68 (52)	43 (35)	

¹Note: Respondents are defined as participants that had a 5-point or greater improvement in St. Marks Score at 24 weeks. Non-respondents are those that had a less-than-5-point improvement in St. Mark's Score at 24 weeks. St. Mark's Score improvement is calculated as the change in score from baseline

²Note: All continuous variable p-values are computed with a t-test. Categorical variables with cell counts < 5 are computed using the Fisher's Exact method, while all other categorical variables are computed using a chi-squared test

SD, standard deviation

Table 3:

Multivariable Logistic Regression Associations of Potential Predictors of St Mark's MID Treatment Response (3a) and Controlling for Adherence at 24 Weeks (3b)

3a: Predictor Variable	Overall p value for predictor	Odds Ratio Point Estimate	Lower 95% CL	Upper 95% CL	P value for OR	P value for treatment x predictor interaction
Treatment Randomization	0.06					
Loperamide/Biofeedback vs. Control		2.13	0.90	5.07	0.09	
Loperamide/Education Only vs. Control		0.93	0.40	2.17	0.86	
Placebo/Biofeedback vs. Control		0.91	0.39	2.16	0.84	
BMI (Categorized)	0.10					0.66
Overweight vs. Normal/Underweight		2.15	1.07	4.34	0.03	
Obese vs. Normal/Underweight		1.62	0.82	3.18	0.17	
Vaginal Estrogen Therapy: No vs. Yes	0.17	1.54	0.83	2.87	0.17	0.81
Anal Sphincter Tone	0.10	1.22	0.96	1.55	0.10	0.92
St. Mark's Score	<0.01	1.20	1.11	1.28	<0.01	0.22

3b: Predictor Variable	Overall p value for predictor	Odds Ratio Point Estimate	Lower 95% CL	Upper 95% CL	P value for OR
Treatment Randomization	0.11				
Loperamide/Biofeedback vs. Control		2.89	0.91	9.19	0.07
Loperamide/Education Only vs. Control		1.13	0.46	2.77	0.80
Placebo/Biofeedback vs. Control		1.25	0.39	3.96	0.71
BMI (Categorized)	0.10				
Overweight vs. Normal/Underweight		2.29	1.07	4.90	0.03
Obese vs. Normal/Underweight		1.75	0.85	3.63	0.13
Vaginal Estrogen Therapy: No vs. Yes	0.49	1.27	0.65	2.50	0.49
Anal Sphincter Tone	0.18	1.19	0.92	1.55	0.18
St. Mark's Score	<0.01	1.22	1.13	1.31	<0.01
Drug Adherence (last time drug was missed) at 24 Weeks	0.03				
Within the past week vs. Never missed		0.35	0.16	0.78	<0.01
1–4 weeks vs. Never missed		0.37	0.15	0.88	0.02
Greater than 1 month vs. Never missed		0.62	0.28	1.34	0.22
Exercise Adherence (last time exercise was missed) at 24 Weeks	0.20				
Within the past week vs. Never missed		0.61	0.23	1.62	0.33
1–4 weeks vs. Never missed		0.93	0.25	3.52	0.92
Greater than 1 month vs. Never missed		2.52	0.56	11.30	0.23

Table 4:

Baseline Clinical, Demographic, and Adherence Characteristics by 50% Reduction Fecal Incontinence Episodes

Measurements	Respondents N=174	Non-Respondents N=82	p-value
Age			0.47
Mean (SD)	63.4 (11.4)	64.4 (9.3)	
BMI kg/m ²			0.43
Mean (SD)	30.0 (6.7)	29.2 (6.9)	
Median (min—max)	28.9 (17—55)	27.9 (17—49)	
BMI (categorized), N (%)			0.24
Normal/Underweight (< 25)	42 (24)	28 (34)	
Overweight (25 – 29)	57 (33)	22 (27)	
Obese (≥ 30)	74 (43)	32 (39)	
Vaginal Deliveries			0.38
Median (min-max)	2 (0 – 7)	2 (0 – 7)	
Vaginal Deliveries (categorized), N (%)			0.98
Yes	153 (88)	72 (88)	
Cesarean Deliveries			0.83
Median (min-max)	0 (0 – 4)	0 (0 – 3)	
Cesarean Deliveries (categorized), N (%)			0.77
Yes	17 (10)	9 (11)	
Menstrual Status, N (%)			0.20
Pre-Menopausal	18 (10)	5 (6)	
Post-Menopausal	145 (83)	75 (92)	
Not sure	11 (6)	2 (2)	
Estrogen Therapy - Vaginal, N (%)			0.33
Yes	41 (24)	24 (29)	
Estrogen Therapy - Oral Patch, N (%)			0.36
Yes	19 (11)	6 (7)	
Current Smoker Status, N (%)			0.64
Yes	12 (7)	7 (9)	
Connective Tissue Disease Status, N (%)			0.11
Yes	10 (6)	1 (1)	
Randomized Treatment, N (%)			<.01
Loperamide with Biofeedback	61 (35)	10 (12)	
Loperamide with Education Only	40 (23)	38 (46)	
Placebo with Biofeedback	52 (30)	20 (24)	
Placebo with Education Only	21 (12)	14 (17)	
Surgery Type, N (%)			
Prior Accidental Bowel Leakage Surgery	9 (5)	3 (4)	0.76

Measurements	Respondents N=174	Non-Respondents N=82	p-value
Prior Rectal or Anal Surgery	28 (16)	6 (7)	0.05
Prior Hysterectomy	86 (49)	40 (49)	0.92
Prior Urinary Incontinence Surgery	45 (26)	23 (28)	0.71
Prior Pelvic Organ Prolapse Surgery	46 (26)	20 (24)	0.73
Bristol Stool Index, N (%)			0.65
Type 1 - Separate hard lumps like nuts	0 (0)	0 (0)	
Type 2 - Sausage shaped but lumpy	25 (14)	10 (12)	
Type 3 - Like a sausage but with cracks on its surface	21 (12)	16 (20)	
Type 4 - Like a sausage or snake, smooth and soft	60 (35)	26 (32)	
Type 5 - Soft blobs with clear cut edges	31 (18)	13 (16)	
Type 6 - Fluffy pieces with ragged edges, a mushy stool	37 (21)	17 (21)	
Type 7 - Watery, no solid pieces	0 (0)	0 (0)	
Average Total Number of Leaks/Week			<0.01
Mean (std)	12.0 (13.0)	8.1 (10.2)	
Fecal Incontinence Type, N (%)			<0.01
Urgency	60 (35)	28 (34)	
Passive	82 (47)	24 (29)	
Both	32 (18)	30 (37)	
Maximum Anal Canal Pressure, Resting (mm/Hg)			0.44
Mean (SD)	40.1 (17.9)	42.1 (20.2)	
Maximum Anal Canal Pressure, Squeeze (mm/Hg)			0.50
Mean (SD)	71.3 (32.5)	74.3 (32.7)	
Anal Sphincter Tone, Squeeze Score			0.99
Mean (SD)	1.9 (1.1)	1.9 (1.1)	
St. Mark's Score			0.01
Mean (SD)	14.6 (4.1)	13.2 (3.9)	
CRADI Score			0.33
Mean (SD)	48.8 (20.2)	51.6 (24.5)	
CRAIQ Score			0.72
Mean (SD)	41.7 (27.2)	43.0 (29.9)	
MMHQ Severity Measures Score			0.17
Mean (SD)	56.6 (24.4)	52.1 (23.8)	
Exercise Adherence (last time exercise was missed) - 24 weeks, N (%)			0.53
Within the past week	58 (49)	17 (52)	
1-2 weeks	9 (8)	6 (18)	
2-4 weeks	4 (3)	1 (3)	
1-3 months	10 (9)	1 (3)	
> 3 months	6 (5)	1 (3)	
Never missed	31 (26)	7 (21)	

Measurements	Respondents N=174	Non-Respondents N=82	p-value
Drug Adherence (last time drug was missed) - 24 weeks, N (%)			0.86
Within the past week	32 (19)	17 (22)	
1–2 weeks	15 (9)	7 (9)	
2–4 weeks	10 (6)	5 (7)	
1–3 months	24 (14)	9 (12)	
> 3 months	11 (7)	8 (10)	
Never missed	77 (46)	31 (40)	

¹Note: Respondents are defined as participants that had a 50% reduction from baseline in FI episodes/day reported on the 24-week bowel diary. Non-respondents are those that had a less-than-50% reduction in FI episodes/day at 24 weeks

²Note: All continuous variable p-values are computed with a t-test. Categorical variables with cell counts < 5 are computed using the Fisher's Exact method, while all other categorical variables are computed using a chi-squared test

SD, standard deviation

Table 5:

Multivariable Logistic Regression Associations of Potential Predictors of 50% Reduction Fecal Incontinence Episodes Treatment Response (5a) and Controlling for Adherence at 24 Weeks (5b)

5a: Predictor Variable	Overall p value for predictor	Odds Ratio Point Estimate	Lower 95% CL	Upper 95% CL	P value for OR	P value for treatment x predictor interaction
Treatment Randomization	0.01					
Loperamide/Biofeedback vs. Control ¹		4.04	1.36	11.98	0.01	
Loperamide/Education Only vs. Control ¹		0.68	0.27	1.76	0.43	
Placebo/Biofeedback vs. Control ¹		1.88	0.69	5.11	0.22	
Prior Rectal Surgery: No vs. Yes	0.17	0.49	0.18	1.37	0.17	0.97
Average Leaks/Week	0.19	1.02	0.99	1.06	0.19	0.41
St. Mark's Score	0.05					0.04
In Loperamide/Biofeedback Group		0.88	0.72	1.06	0.18	
In Loperamide/Education Only Group		1.02	0.90	1.16	0.73	
In Placebo/Biofeedback Group		1.16	1.00	1.34	0.05	
In Control Group		1.29	1.01	1.65	0.045	
MMHQ Severity Score	0.88	1.00	0.99	1.02	0.88	0.14
Fecal Incontinence - Leak Type	0.01					0.67
Urge vs. Both		2.39	1.09	5.25	0.03	
Passive vs. Both		3.26	1.48	7.17	<0.01	

5b: Predictor Variable	Overall p value for predictor	Odds Ratio Point Estimate	Lower 95% CL	Upper 95% CL	P value for OR
Treatment Randomization	0.04				
Loperamide/Biofeedback vs. Control		4.18	1.11	15.78	0.03
Loperamide/Education Only vs. Control		0.76	0.30	1.91	0.55
Placebo/Biofeedback vs. Control		1.75	0.49	6.22	0.39
Prior Rectal Surgery: No vs. Yes	0.14	0.46	0.16	1.29	0.14
Average Leaks/Week	0.32	1.02	0.99	1.05	0.32
St. Mark's Score ²	0.11	1.07	0.99	1.17	0.11
MMHQ Severity Score	0.88	1.00	0.99	1.01	0.88
Fecal Incontinence - Leak Type	0.02				
Urge vs. Both		2.20	1.00	4.85	0.05
Passive vs. Both		3.02	1.38	6.62	<0.01
Drug Adherence (last time drug was missed) at 24 Weeks	0.94				
Within the past week vs. Never missed		0.81	0.35	1.86	0.62
1-4 weeks vs. Never missed		1.00	0.40	2.52	1.00

5b:Predictor Variable	Overall p value for predictor	Odds Ratio Point Estimate	Lower 95% CL	Upper 95% CL	P value for OR
Greater than 1 month vs. Never missed		0.83	0.36	1.90	0.65
Exercise Adherence (last time exercise was missed) at 24 Weeks	0.36				
Within the past week vs. Never missed		1.07	0.34	3.36	0.91
1–4 weeks vs. Never missed		0.47	0.11	1.98	0.30
Greater than 1 month vs. Never missed		2.32	0.38	14.32	0.36

¹Odds ratios for treatment groups were evaluated at the mean baseline St. Mark's score of 14.2

²The interaction between treatment group and baseline St. Mark's score was not statistically significant in the model controlling for treatment adherence and was not included in the final model