Impact of treatment for Fecal Incontinence on Constipation Symptoms

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Condensation
Improvements in constipation symptoms in women following treatment of fecal incontinence are small, and not significantly different whether or not they were treated with loperamide.

Short version of title: Defecatory Symptoms and Fecal Incontinence

AJOG at a Glance
A. Why was this study conducted?
- Loperamide, a medication widely used for the treatment of fecal incontinence, can worsen defecatory symptoms. The goal of this study was to compare changes in constipation symptoms in women undergoing treatment for fecal incontinence with education only, loperamide, anal sphincter exercises with biofeedback, or both loperamide and biofeedback.

B. What are the key findings?
- There were small improvements in constipation symptoms which were not different between treatment groups.
- Women with improved fecal incontinence symptoms had greater improvement in constipation symptoms than women that did not have improvement in fecal incontinence symptoms.

C. What does this study add to what is already known?
- Findings of this study should reassure clinicians that among women with normal stool consistency, treatment of fecal incontinence with loperamide does not worsen constipation symptoms.

Key Words: Fecal Incontinence, defecatory symptoms, constipation, anorectal disorders, loperamide, anal exercises with biofeedback,
Abstract

Objective: Defecatory symptoms, such as sense of incomplete emptying and straining with bowel movements, are paradoxically present in women with fecal incontinence (FI). Treatments for FI, such as loperamide and biofeedback, can worsen or improve defecatory symptoms, respectively. The primary aim of this study was to compare changes in constipation symptoms in women undergoing treatment for FI with education only, loperamide, anal muscle exercises with biofeedback, or both loperamide and biofeedback. Our secondary aim was to compare changes in constipation symptoms among responders and non-responders to FI treatment.

Methods: This was a planned secondary analysis of a randomized controlled trial comparing 2 first-line therapies for FI in a 2x2 factorial design. Women with at least monthly FI and normal stool consistency were randomized to 4 groups: 1) oral placebo plus education only, 2) oral loperamide plus education only, 3) placebo plus anorectal manometry-assisted biofeedback and 4) loperamide plus biofeedback. Defecatory symptoms were measured using the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire at baseline, 12 weeks and 24 weeks. The PAC-SYM consists of 12 items that contribute to a global score and 3 subscales: stool characteristics/symptoms (hardness of stool, size of stool, straining, inability to pass stool), rectal symptoms (burning, pain, bleeding, incomplete bowel movement), and abdominal symptoms (discomfort, pain, bloating, cramps). Scores for each subscale as well as the global score range from 0 (no symptoms) to 4 (maximum score), with negative change scores representing improvement in defecatory symptoms. Responders to FI treatment were defined as women with a minimally important clinical improvement of ≥5-points on the St. Mark’s
Intent-to-treat analysis was performed using a longitudinal mixed model, controlling for baseline scores, to estimate changes in PAC-SYM scores from baseline through 24 weeks.

**Results:** At 24 weeks, there were small changes in PAC-SYM global scores in all four groups: oral placebo plus education (-0.3; 95% CI -0.5, -0.1), loperamide plus education (-0.1, 95% CI -0.3, 0.0), oral placebo plus biofeedback (-0.3, 95% CI -0.4, -0.2), and loperamide plus biofeedback (-0.3, 95% CI -0.4, -0.2). No differences were observed in change in PAC-SYM scores between women randomized to placebo plus education and those randomized to loperamide plus education (p=0.17) or placebo plus biofeedback (p=0.82). Change in PAC-SYM scores in women randomized to combination loperamide plus biofeedback therapy was not different from that of women randomized to treatment with loperamide or biofeedback alone. Responders had greater improvement in PAC-SYM scores than non-responders (-0.4; 95% CI -0.5, -0.3 vs. -0.2; 95% CI -0.3, -0.0, p<0.01, mean difference 0.2, 95% CI 0.1, 0.4).

**Conclusion:** Change in constipation symptoms following treatment of FI in women are small and are not significantly different between groups. Loperamide treatment for FI does not worsen constipation symptoms among women with normal consistency stool. Women with clinically significant improvement in FI symptoms report greater improvement in constipation symptoms.
Defecatory symptoms, especially those associated with constipation, are paradoxically common in women with fecal incontinence. In a series of 262 subjects, 36% of patients presenting primarily with constipation reported fecal incontinence while 34% of subjects presenting primarily with fecal incontinence reported symptoms of constipation (1). The quality of life of subjects with coexisting constipation and fecal incontinence is also significantly worse than either symptom alone (2). The presence of defecatory symptoms such as straining to defecate, feeling of incomplete bowel evacuation, digitation, sensation of blockage, and constipation indicate the presence of an underlying defecation dysfunction. Manometry studies have shown that potential markers of defecation dysfunction, such as poor rectal compliance, are common in women with FI (3). Thus, it is important that providers treating FI understand potential implications of therapies on commonly-coexisting defecatory symptoms.

First line treatments for FI include constipating medications, such as loperamide, and pelvic floor physical therapy, with or without anorectal biofeedback. Loperamide has been shown to reduce incontinence episodes and improve symptoms and quality of life but can exacerbate constipation symptoms (4, 5). Pelvic floor physical therapy and anorectal biofeedback have been shown to improve defecatory symptoms such as straining and splinting for bowel movements (6). Despite the common coexistence of FI and defecatory symptoms and the potential impact of treatments of FI on defecatory symptoms, well-designed prospective studies exploring the relationship between defecatory symptoms and response to treatment for FI are lacking.
We conducted a planned secondary analysis to the Controlling Anal incontinence by Performing Anal Exercises with Biofeedback or Loperamide (CAPABLe) trial (7) to determine the impact of first-line treatments for FI on constipation symptoms. Our primary aim was to compare the changes in constipation symptoms in women randomized to treatment for FI with education only, loperamide, anal muscle exercises with biofeedback, or both loperamide and biofeedback. Our secondary aim was to compare changes in constipation symptoms among women who reported improved FI symptoms and those who did not report improvement in FI symptoms following treatment.

**Materials and Methods**

The CAPABLe trial is a randomized controlled factorial trial conducted between April 2014 and April 2016 at 8 sites participating in the Pelvic Floor Disorders Network, sponsored by Eunice Kennedy Shriver National Institute of Child Health and Human Development. The study design has been previously published (8). Women with bothersome FI occurring at least monthly over the preceding 3 months were invited 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. All sites received IRB approval and all participants gave written informed consent (Clinicaltrials.gov NCT02008565).

Enrolled participants underwent a single randomization using a 0.5:1:1:1 allocation to one of four treatment combinations: 1) oral placebo plus education only, 2) oral loperamide plus education only, 3) oral placebo plus anal sphincter exercise training using manometry-
assisted biofeedback, and 4) oral loperamide plus anal sphincter exercise training using manometry-assisted biofeedback. All participants were provided education consisting of the 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 discusses symptoms, causes, diagnosis, and treatments including dietary treatment for bowel control problems.

Participants not randomized to biofeedback had baseline, 12 and 24 week visits. Participants randomized to biofeedback had visits at baseline, 2, 4, 6, 9, 12 and 24 weeks. Participants randomized to the biofeedback group received an individualized program that included diagnostic anorectal manometry (ARM) evaluation, biofeedback strength training and sensory or urge resistance training (mcompass, Medspira, Minneapolis, MN). Biofeedback participants were prescribed a home exercise program based on their individual performance during the intervention visits. All study interventionists underwent standardized training (9).

Participants initially received placebo or 2 mg of oral loperamide (1 capsule) per day with the option of dose escalation up to a maximum of 4 capsules daily and the option of dose reduction due to adverse effects to 1 capsule every other day. Dose escalation, maintenance or reduction was based on balancing efficacy and side effects of treatment using two Likert scales: the Patient Global Symptom Control rating scale (PGSC), “My current treatment is giving me adequate control of my stool leakage” and the Patient Global Tolerability rating Scale (PGTS), “My current medication is giving me bothersome side effects.” Responses on both scales ranged from 1, ‘disagree strongly’ to 5, ‘agree strongly.’ Those women reporting inadequate control of stool leakage and bothersome side effects were instructed to discontinue the study medication
but were requested to remain in the study follow-up for the duration. Participants reporting deterioration in FI symptoms after discontinuing the study drug due to side effects were allowed to re-start study drug after an assessment by the site investigator.

The primary outcome for CAPABLe was the change from baseline to 24 weeks in the St. Mark’s (Vaizey) FI severity scale. The primary outcome for this secondary study was change from baseline to 24 weeks in the Patient Assessment of Constipation Symptoms (PAC-SYM) global score (10). The PAC-SYM consists of 12 items that contribute to a global score and 3 subscales: stool characteristics/symptoms (hardness of stool, size of stool, straining, inability to pass stool), rectal symptoms (burning, pain, bleeding, incomplete bowel movement), and abdominal symptoms (discomfort, pain, bloating, cramps). Subscales and global scores range from 0 (no symptoms) to 4 (maximum score), with decreasing scores representing improvement in defecatory symptoms. The minimal important difference (MID) for the PAC-SYM questionnaire is -0.6 (21). Secondary outcomes included change from baseline to 24 weeks in the PAC-SYM subscale scores. Throughout the study, outcome evaluators were masked to the treatment assignment for the biofeedback intervention. Participants and all study staff other than the research pharmacist were masked to the medication assignment.

A responder-to-treatment was defined as any subject that showed the minimally important clinical difference, at least a 5-point decrease, in the St. Mark’s (Vaizey) score at 24 weeks (11).

Statistical Analysis
Women who had constipation symptom outcome data at 12 or 24 weeks were included in analysis. The change from baseline in PAC-SYM global scores at 24 weeks was analyzed using a general linear mixed model. Independent variables included baseline PAC-SYM global score, treatment assignments, interactions between drug and exercise, week 12 or 24, interactions between week and treatment, and clinical site. The model accounted for the dependence between repeated measurements on the same subject by modeling the within-participant covariance structure. Combination treatment (oral loperamide plus anal sphincter exercise training using manometry-assisted biofeedback) was compared to oral loperamide plus education only or oral placebo plus biofeedback alone. Oral loperamide plus education only was compared to oral placebo plus education only, and oral placebo plus biofeedback was compared to oral placebo plus education only. Each comparison was evaluated at a type I error level of 0.05. Box plots were used to explore the relationship between baseline stool consistency (Bristol stool type) and change in PAC-SYM scores from baseline for each treatment group.

The change from baseline in PAC-SYM global score at 24 weeks was also compared between responders-to-treatment and non-responders. The baseline PAC-SYM global score was first compared between responders and non-responders using a general linear model with responder status and clinical site as independent variables. The change from baseline in PAC-SYM global scores at 24 weeks was compared for responders and non-responders using a general linear mixed model with responder status, treatment assignments, week 12 or 24, clinical site, and interactions between drug and exercise, week and treatment, and responder status and week as independent variables. The model accounted for the dependence between
repeated measurements on the same subject by modeling the within-participant covariance structure. Responders were compared to non-responders at a type I error level of 0.05.

Subjects without 24-week data available for the St. Mark’s (Vaizey) score were excluded from the analysis comparing responders and non-responders.

The other secondary outcomes, changes in PAC-SYM subscales, were evaluated similarly for both comparisons between treatments and between responders and non-responders. Primary and secondary outcomes were analyzed using a modified intent-to-treat principle, with the limitation that only observed outcomes at 12 and 24 weeks were included in analysis. No adjustments were made for performing multiple statistical tests.

**Results**

In the CAPABLE trial, 296 eligible women were randomized to the following groups: oral placebo plus education (n=42), loperamide plus education (n=86), oral placebo plus biofeedback (n=83) and the combined intervention of loperamide plus biofeedback (n=85).

Over 83% of participants had defecatory symptom outcome data at 12 or 24 weeks and were included in analysis: oral placebo plus education 35/42 (83%), loperamide plus education 71/86 (83%), oral placebo plus biofeedback 69/83 (83%), and loperamide plus biofeedback, 72/85 (85%).

Baseline demographic and clinical characteristics of participants included in this analysis are presented in Table 1. As expected in a randomized trial, women randomized to placebo plus education did not differ significantly from women randomized to loperamide plus education or
oral placebo plus biofeedback. Similarly, baseline characteristics of women who received both active treatments (loperamide plus biofeedback) were not different from women who received one active treatment (loperamide plus education or placebo plus biofeedback) only. Baseline PAC-SYM scores were similar in all groups.

All groups demonstrated small improvements in global PAC-SYM scores at 24 weeks:

oral placebo plus education (-0.3, 95% CI -0.5, -0.1), loperamide plus education (-0.1, 95% CI -0.3, 0.0), oral placebo plus biofeedback (-0.3, 95% CI -0.4, -0.2) and loperamide plus biofeedback (-0.3, 95% CI -0.4, -0.2). No differences in improvement in PAC-SYM global scores between women randomized to placebo plus education and women randomized to loperamide plus education or oral placebo plus biofeedback were observed (Table 2). Improvement in PAC-SYM global scores in women randomized to combination loperamide plus biofeedback therapy was also not significantly different from improvement in women randomized to loperamide or biofeedback alone (Table 3). Likewise, no differences between groups were noted in the subscales of the PAC-SYM with the exception of the rectal subscale when comparing loperamide plus biofeedback to loperamide plus education. No associations or patterns that might support an association between baseline stool consistency and improvement or worsening of PAC-SYM scores for any of the treatment groups were observed in visual box plots (data not shown).

Of the women with FI symptom outcome data at 24 weeks, 137 had clinically significant improvement in Vaizey score (responders) and 129 did not (non-responders). Of these women, 124/137 (91%) of responders and 119/129 (92%) of non-responders had PAC-SYM defecatory symptom outcomes available at either 12 or 24 weeks. Responders had greater improvement in
global PAC-SYM scores at 24 weeks than non-responders (-0.4; 95% CI -0.5, -0.3 vs. -0.2; 95% CI -0.3, -0.0, mean difference 0.2, 95% CI 0.1, 0.4) despite similar scores at baseline (Tables 4 and 5). Responders had greater improvement in the all subscales of the PAC-SYM (Table 5).

Comments

Principal Findings

We did not find differences in change in constipation symptoms among women with at least monthly FI and normal stool consistency randomized to loperamide and/or biofeedback compared to placebo plus education. Women who reported improvement in FI symptoms had greater improvement in constipation symptoms as measured by the PAC-SYM compared to those with no improvement in FI symptoms. These findings are useful in understanding the relationship between defecatory symptoms and FI treatments, and provide clinical reassurance that the use of loperamide in women with FI with normal stool consistency does not worsen constipation symptoms as all groups had small improvements in constipation symptoms.

Results, Clinical and Research Implications

Defecatory symptoms commonly co-exist in women with FI. Several retrospective or cross-sectional community-based studies and surveys in urogynecology clinics demonstrate a significant association between constipation that includes defecatory symptoms and FI (12-15). Studies have also demonstrated that coexisting constipation can modify the response to treatment for fecal incontinence. In a retrospective study of 145 patients treated for FI using
biofeedback, symptoms such as straining with bowel movements, use of splinting, and
abnormal rectal compliance on anorectal manometry were significantly more common in
women who had poor response to treatment (6). Despite lack of controlled studies, clinical
guidelines recommend treating women with co-existing FI and underlying evacuation disorders
with interventions such as biofeedback to train patients to relax their pelvic floor (16).
Unfortunately, these studies and recommendations have not been prospectively studied to
assess treatment effect and did not use valid and reliable defecatory symptom-severity scales.

In contrast, our study demonstrated that defecatory symptoms do not worsen with
treatment with either loperamide or anal muscles exercises with biofeedback and suggest there
may be marginal improvement. The biofeedback training protocol in this study included
instruction on recto-anal coordination which may have improved evacuation of the rectum.
However, it is unclear why women randomized to loperamide did not report higher defecatory
symptom severity after treatment compared to women not taking loperamide. One possibility
is that loperamide improved stool consistency and this improved efficiency of evacuation.
However, we did not notice any association between baseline stool consistency and change in
PAC-SYM score in women who received loperamide. Another possible explanation is that
loperamide, which in addition to established effects on improving stool consistency, has been
shown to affect rectal perception and increase anal sphincter resting and squeeze pressure
impacts defecatory symptoms through these mechanisms.(17,18) When anal sphincter
pressures are low, stool in the anorectum is sensed at lower volumes (18); thus our findings
suggest that loperamide’s effect on increasing sphincter pressure may result in changes in
visceral sensitivity leading to improvement in symptoms such as sense of incomplete emptying.
Greater improvement in defecatory symptoms in responders compared to non-responders may suggest shared underlying mechanisms between FI and defecatory dysfunction. Women with FI have been shown to have poor rectal compliance indicating the presence of co-existing defecatory dysfunction (3). Additionally, women with symptoms of defecatory dysfunction such as straining for bowel movements and sense of incomplete evacuation, have weaker axial forces not only during expulsion but also during contraction of the pelvic floor muscles, suggesting an increased risk for FI (19). In women where treatments affect these underlying mechanisms, both FI and defecatory symptoms may improve.

Alternatively, our finding may reflect the significant impact of functional anorectal disorders on quality of life. In a prior study examining the risk factors for constipation and FI, poor self-rated health and depression were found to be common risk factors for both conditions (20). Thus, women who had improvement in FI severity may have perceived overall subjective improvement in quality of life including defecatory symptoms.

**Strengths and Limitations**

The strengths of this study include the prospective study design of women randomly assigned to the two common conservative treatments for FI. Defecatory symptoms were evaluated using a valid, reliable and responsive questionnaire that has been used in other clinical trials to assess patient-reported defecatory dysfunction. Despite the large sample size adequately powered for the primary study (7), there was limited power to detect marginal differences between the combined versus individual treatments and single treatment versus control groups. The study findings are generalizable to women with normal stool consistency who are seeking treatment for FI rather than constipation symptoms and the study did not
collect additional objective measures of defecatory dysfunction such as transit studies or balloon testing. Additionally, we excluded women with large rectoceles and we did not assess for high tone dysfunction, two conditions that could impact constipations symptoms and as such our data may not be generalizable to women with those conditions. Further, although all intervention groups as well as the responder group had defecatory symptom improvements compared to baseline, the change in scores did not meet the minimal important difference (MID, -0.6) for the PAC-SYM questionnaire (21). The concept of MID, the smallest difference in score associated with a clinically meaningful improvement, is frequently used in clinical trials to determine whether the difference observed is not only statistically significant but also clinically relevant. The proposed MID of 0.6 for the PAC-SYM was derived from trials evaluating the treatment efficacy of a medication for chronic constipation. Therefore, the improvement in defecatory symptoms observed in the current study may not have the same magnitude of change in symptoms compared to the clinical trials evaluating the treatment of constipation.

**Conclusion**

In summary, women seeking treatment for FI had modest improvements in defecatory symptoms, regardless of treatment group. These improvements were more marked in women who reported improvement in FI. In contrast to other studies, the addition of loperamide did not have a negative impact on defecatory symptoms.
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References


Table 1. Demographics: Baseline clinical and demographic characteristics of participants in placebo, individual treatment, and combined treatment groups.

<table>
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<tr>
<th>Endpoint</th>
<th>Category</th>
<th>Placebo - Education Only (N=35)</th>
<th>Loperamide - Education Only (N=71)</th>
<th>Placebo - Exercise plus Biofeedback (N=69)</th>
<th>Loperamide - Exercise plus Biofeedback (N=72)</th>
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<tr>
<td></td>
<td></td>
<td>Baseline Characteristic</td>
<td>Baseline Characteristic</td>
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<tr>
<td>Age, mean (SD) [min, max], y</td>
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<td>62.5 (10.5) [40.2, 83.3]</td>
<td>62.5 (10.7) [38.1, 83.3]</td>
<td>65.5 (10.3) [39.7, 93.4]</td>
<td>63.6 (12.4) [27.5, 87.6]</td>
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<td>2 (2.8)</td>
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<td>59 (83.1)</td>
<td>56 (77.8)</td>
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<td>61 (88.4)</td>
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<td>1 (1.4)</td>
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<td>1 (1.4)</td>
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<td>Prior rectal or anal surgery, No. (%)</td>
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<td>6 (8.6)</td>
<td>12 (17.1)</td>
<td>8 (11.6)</td>
</tr>
<tr>
<td>BMI, mean (SD) [min, max]</td>
<td></td>
<td>30.5 (9.0) [20.2, 62.1]</td>
<td>31.0 (6.7) [20.2, 48.5]</td>
<td>29.9 (6.7) [19.5, 55.0]</td>
<td>28.8 (6.6) [17.1, 43.2]</td>
</tr>
<tr>
<td>Dietary Fiber Score, mean (SD) [min, max]</td>
<td></td>
<td>15.1 (7.3) [2.0, 33.0]</td>
<td>15.3 (6.3) [4.0, 31.0]</td>
<td>16.5 (6.4) [4.0, 41.0]</td>
<td>16.1 (5.8) [5.0, 29.0]</td>
</tr>
<tr>
<td>Daily fiber intake, mean (SD) [min, max]</td>
<td></td>
<td>14.6 (5.4) [4.9, 27.8]</td>
<td>14.7 (4.7) [6.4, 26.3]</td>
<td>15.6 (4.7) [6.4, 33.7]</td>
<td>15.3 (4.3) [7.1, 24.9]</td>
</tr>
<tr>
<td>Bristol Stool Index, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2. Sausage shaped but lumpy</td>
<td></td>
<td>6 (17.1)</td>
<td>6 (8.5)</td>
<td>16 (22.2)</td>
<td>5 (7.2)</td>
</tr>
<tr>
<td>Type 3. Like a sausage or snake but with cracks on</td>
<td></td>
<td>2 (5.7)</td>
<td>14 (19.7)</td>
<td>9 (12.5)</td>
<td>10 (14.5)</td>
</tr>
<tr>
<td>Type 4. Like a sausage or snake, smooth and soft</td>
<td></td>
<td>14 (40.0)</td>
<td>24 (33.8)</td>
<td>20 (27.8)</td>
<td>25 (36.2)</td>
</tr>
<tr>
<td>Type 5. Soft blobs with clear cut edges</td>
<td></td>
<td>5 (14.3)</td>
<td>13 (18.3)</td>
<td>12 (16.7)</td>
<td>15 (21.7)</td>
</tr>
<tr>
<td>Type 6. Fluffy pieces with ragged edges, a mushy s</td>
<td></td>
<td>8 (22.9)</td>
<td>14 (19.7)</td>
<td>15 (20.8)</td>
<td>14 (20.3)</td>
</tr>
<tr>
<td>Rome III IBS Clinical Status, No. (%)</td>
<td></td>
<td>5 (14.3)</td>
<td>14 (19.7)</td>
<td>14 (19.4)</td>
<td>15 (21.7)</td>
</tr>
</tbody>
</table>
## Endpoint Category

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Baseline Characteristic</th>
<th>Baseline Characteristic</th>
<th>Baseline Characteristic</th>
<th>Baseline Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC-SYM Scores, mean (SD) [min, max]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool Score</td>
<td>1.1 (0.8) [0.0, 2.6]</td>
<td>1.2 (0.8) [0.0, 2.8]</td>
<td>0.9 (0.9) [0.0, 3.8]</td>
<td>1.1 (0.8) [0.0, 2.8]</td>
</tr>
<tr>
<td>Rectal Score</td>
<td>0.8 (0.8) [0.0, 2.7]</td>
<td>0.7 (0.7) [0.0, 2.7]</td>
<td>0.9 (0.7) [0.0, 3.3]</td>
<td>0.7 (0.7) [0.0, 2.3]</td>
</tr>
<tr>
<td>Abdominal Score</td>
<td>1.0 (1.1) [0.0, 3.5]</td>
<td>1.1 (0.9) [0.0, 3.3]</td>
<td>1.1 (0.8) [0.0, 3.4]</td>
<td>0.9 (0.8) [0.0, 3.0]</td>
</tr>
<tr>
<td>Global Score</td>
<td>1.0 (0.7) [0.0, 2.7]</td>
<td>1.1 (0.7) [0.0, 2.6]</td>
<td>0.7 (0.8) [0.0, 3.0]</td>
<td>0.9 (0.6) [0.0, 2.5]</td>
</tr>
</tbody>
</table>
Table 2. Change in PAC-SYM at 24 weeks for Placebo versus Loperamide and Placebo versus Biofeedback

<table>
<thead>
<tr>
<th>Change in PAC-SYM Score</th>
<th>Placebo - Education (N=35)</th>
<th>Loperamide - Education (N=71)</th>
<th>Placebo - Biofeedback (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Change from Baseline(95% CI)</td>
<td>Mean Change from Baseline(95% CI)</td>
<td>P-value for Comparison</td>
</tr>
<tr>
<td>Change in PAC-SYM Abdominal Score</td>
<td>-0.4 (-0.7, -0.2)</td>
<td>-0.2 (-0.3, 0.0)</td>
<td>0.052</td>
</tr>
<tr>
<td>Change in PAC-SYM Rectal Score</td>
<td>-0.3 (-0.5, -0.1)</td>
<td>-0.1 (-0.2, 0.0)</td>
<td>0.125</td>
</tr>
<tr>
<td>Change in PAC-SYM Stool Score</td>
<td>-0.2 (-0.4, 0.0)</td>
<td>-0.2 (-0.3, 0.0)</td>
<td>0.878</td>
</tr>
<tr>
<td>Change in PAC-SYM Global Score</td>
<td>-0.3 (-0.5, -0.1)</td>
<td>-0.1 (-0.3, 0.0)</td>
<td>0.169</td>
</tr>
</tbody>
</table>

Table 3: Change in PAC-SYM at 24 weeks for Combined Loperamide and Biofeedback versus Loperamide only and Biofeedback only

<table>
<thead>
<tr>
<th>Change in PAC-SYM Score</th>
<th>Loperamide - Biofeedback (N=72)</th>
<th>Loperamide - Education (N=71)</th>
<th>Placebo - Biofeedback (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Change from Baseline(95% CI)</td>
<td>Mean Change from Baseline(95% CI)</td>
<td>P-value for Comparison</td>
</tr>
<tr>
<td>Change in PAC-SYM Abdominal Score</td>
<td>-0.3 (-0.5, -0.1)</td>
<td>-0.2 (-0.3, 0.0)</td>
<td>0.257</td>
</tr>
<tr>
<td>Change in PAC-SYM Rectal Score</td>
<td>-0.4 (-0.5, -0.1)</td>
<td>-0.1 (-0.2, 0.0)</td>
<td>0.010</td>
</tr>
<tr>
<td>Change in PAC-SYM Stool Score</td>
<td>-0.2 (-0.4, 0.0)</td>
<td>-0.2 (-0.3, 0.0)</td>
<td>0.549</td>
</tr>
<tr>
<td>Change in PAC-SYM Global Score</td>
<td>-0.3 (-0.4, -0.2)</td>
<td>-0.1 (-0.3, 0.0)</td>
<td>0.147</td>
</tr>
</tbody>
</table>
Table 4. Baseline PAC-SYM scores in responders and non-responders to treatment for FI

<table>
<thead>
<tr>
<th>Baseline PAC-SYM Score</th>
<th>Responders (N=124)</th>
<th>Non-Responders (N=119)</th>
<th>P-value for Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC-SYM Abdominal Score</td>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
<td></td>
</tr>
<tr>
<td>1.06 (0.89, 1.23)</td>
<td>0.88 (0.70, 1.06)</td>
<td></td>
<td>0.127</td>
</tr>
<tr>
<td>PAC-SYM Rectal Score</td>
<td>0.67 (0.52, 0.81)</td>
<td>0.67 (0.52, 0.81)</td>
<td>0.992</td>
</tr>
<tr>
<td>PAC-SYM Stool Score</td>
<td>1.10 (0.95, 1.25)</td>
<td>1.14 (0.99, 1.30)</td>
<td>0.675</td>
</tr>
<tr>
<td>PAC-SYM Global Score</td>
<td>0.98 (0.85, 1.11)</td>
<td>0.94 (0.80, 1.07)</td>
<td>0.641</td>
</tr>
</tbody>
</table>

Table 5. Change in PAC-SYM scores at 24 weeks in responders and non-responders to treatment for FI

<table>
<thead>
<tr>
<th>Change in PAC-SYM Score</th>
<th>Responders (N=124)</th>
<th>Non-Responders (N=119)</th>
<th>P-value for Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in PAC-SYM Abdominal Score</td>
<td>-0.48 (-0.63, -0.32)</td>
<td>-0.17 (-0.33, -0.01)</td>
<td>0.005</td>
</tr>
<tr>
<td>Change in PAC-SYM Rectal Score</td>
<td>-0.37 (-0.50, -0.24)</td>
<td>-0.16 (-0.29, -0.03)</td>
<td>0.020</td>
</tr>
<tr>
<td>Change in PAC-SYM Stool Score</td>
<td>-0.34 (-0.47, -0.20)</td>
<td>-0.13 (-0.26, 0.01)</td>
<td>0.022</td>
</tr>
<tr>
<td>Change in PAC-SYM Global Score</td>
<td>-0.39 (-0.50, -0.28)</td>
<td>-0.15 (-0.26, -0.03)</td>
<td>0.002</td>
</tr>
</tbody>
</table>