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Randomized Multicenter Clinical Trial of Myofascial Physical Therapy in Women with Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS) and Pelvic Floor Tenderness

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Abstract

Objectives—To determine the efficacy and safety of pelvic floor Myofascial Physical Therapy (MPT) in women with newly-symptomatic IC/PBS, as compared to Global Therapeutic Massage (GTM).

Materials and Methods—A randomized controlled trial of 10 scheduled treatments of MPT vs. GTM was performed at 11 clinical centers located in North America. We recruited women with IC/PBS with demonstrable pelvic floor tenderness on physical examination and a limitation of no

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more than 3 years symptom duration. The primary outcome was the proportion of responders defined as 'moderately improved' or 'markedly improved' in overall symptoms compared to baseline on a 7-point scale Global Response Assessment (GRA). Secondary outcomes included ratings for pain, urgency, frequency; the O'Leary-Sant IC Symptom and Problem Index (ICSI/ICPI) and reports of adverse events. We compared response rates between treatment arms using the exact conditional version of the Mantel-Haenszel test to control for clustering by clinical center. For secondary efficacy outcomes, cross-sectional descriptive statistics and changes from baseline were calculated.

Results—Eighty-one women randomized to the two treatment groups had similar symptoms at baseline. The GRA response rate was 26% in the GTM group and 59% in the MPT group (p=0.0012). Pain, urgency, and frequency ratings and in ICSI/ICPI decreased in both groups during follow-up and were not significantly different between the groups. Pain was the most common adverse event, occurring at similar rates in both groups. There were no serious adverse events reported.

Conclusions—A significantly higher proportion of women with IC/PBS reponded to treatment with MPT than with GTM. MPT may be a beneficial therapy in women with this syndrome.

Keywords

Urologic Pelvic Pain Syndrome; Interstitial Cystitis; Painful Bladder Syndrome; Physical Therapy

Introduction

Treatment of interstitial cystitis/painful bladder syndrome (IC/PBS) remains suboptimal. The clinical course of IC/PBS can be highly variable, however most patients display tension and tenderness of the pelvic floor musculature and other somatic tissues.[1-8] Frequently-found abnormalities include muscular tenderness and connective tissue restrictions of muscle, fascia, and subcutaneous tissues of the pelvic floor, hip girdle and abdominal wall. These somatic abnormalities may contribute to the pain of IC/PBS. There is suggestive evidence that treatment of these tissue abnormalities using myofascial physical therapy (MPT) techniques can significantly relieve symptoms of IC/PBS.[4, 5, 9]

We previously reported the findings of a multi-center, randomized feasibility study comparing specialized pelvic floor MPT to treatment with nonspecific global therapeutic massage (GTM) for relief of symptoms in patients with IC/PBS or CP/CPPS.[9] In that study, the benefit of MPT over GTM was most marked for patients with IC/PBS, almost all of whom were women. We were able to standardize both treatments across multiple study sites and found that patients readily accepted study treatments. Among patients with IC/PBS the response rate was 50% in the MPT group and 7% in the GTM group suggesting that MPT may be a useful treatment for this syndrome.

Based on the findings from our pilot study we conducted a second study to further compare the efficacy and safety and durability of MPT to GTM in women with IC/PBS.

Methods

We conducted a randomized, single-blind, randomized clinical trial comparing pelvic floor MPT to GTM. The design and methods of this randomized trial are identical to those described previously for our feasibility study[9] with the exception that, in this study, recruitment was limited to women.

Female patients were eligible for inclusion if they had a clinical diagnosis of IC/PBS, and recorded ratings for bladder pain, frequency, and urgency each at a usual level of at least 3

on a 0-10 scale, present for at least three months but not longer than 3 years. Baseline symptom ratings were recorded twice, two weeks apart, and the average rating of symptom severity was used to determine study eligibility. An additional eligibility requirement was the finding of pelvic floor tenderness during vaginal examination by the study physician, confirmed by the study physical therapist.

Women were excluded if they had not previously undergone at least one course of a standard therapy for IC/PBS or if they had previously received treatment with pelvic floor MPT. Those who met eligibility criteria at baseline screening were randomized equally to either MPT or to GTM. The goal of randomizing 88 subjects (44 per treatment arm) at 11 clinical centers, with 4-5 participants at each center, was chosen to provide 80% power to detect a difference of 30% in the response rates, assuming a rate for GTM of 10% as shown in our pilot study. Those randomized to MPT received targeted internal and external tissue manipulation focusing on the muscles and connective tissues of the pelvic floor, hip girdle, and abdomen. The MPT methodology has been described in detail previously.[9] The GTM treatment followed a traditional full-body Western massage program.[10] Physical therapists from each site were centrally trained and certified in the performance of both interventions to standardize treatment. Subjects received up to ten, 60-minute treatment sessions over a 12-week time period. Subjects were not informed whether the treatment they were receiving was MPT or GTM. No other changes in urologic care occurred during the course of the study.

Physician examiners and research nurses collecting outcome data were masked to treatment assignment. Outcomes related to symptom improvement were assessed at 12 weeks (at the completion of the treatment phase) and were planned again three months later during a follow-up phase. Adverse events were recorded weekly during the treatment phase of the study. After completion of the treatment intervention phase of the study, subjects were permitted to obtain physical therapy or any other IC/PBS treatment through their usual healthcare provider if they desired. Similar to our previous study, **t**he primary outcome of the study was the proportion of responders at 12 weeks after study initiation or at study withdrawal, based on a Global Response Assessment (GRA).[9] The GRA queries “As compared to when you started the current study, how would you rate your overall symptoms now?” The seven response options are “markedly worse”, “moderately worse”, “slightly worse”, “the same”, “slightly improved”, “moderately improved”, and “markedly improved.” Participants who indicated they were “moderately” or “markedly” improved were considered responders. Subjects who withdrew from study for any reason, and who did not provide data on the primary outcome, were considered treatment non-responders, and included in denominators for calculation of response rates.

A wide range of secondary outcomes were also measured including patient ratings of bladder pain, urgency, and frequency on scales with a range of 0-10, urinary frequency and volume measures obtained from a 24-hour voiding diary, the IC Symptom and Problem Index (ICSI and ICPI),[11] the Health Status Questionnaire (SF-12),[12] Female Sexual Functioning Index 2000 (FSFI),[13] and the Female Symptom Questionnaire (FSQ).[14]

Descriptive statistics were produced by treatment arm for baseline demographics and symptom measures. Comparisons of distributions of these baseline characteristics between treatment groups, to evaluate the balance of the randomization, used Fisher's exact tests, exact Kruskal-Wallis tests (for ordered categories), or exact Wilcoxon rank-sum tests. Descriptive statistics were also produced for patient study status (completed, on-going, or withdrawn). Comparisons of overall adverse event rates, classifying each patient once according to worst grade reported across all body systems, were performed using an exact Kruskal-Wallis test.

The primary outcome analysis compared response rates between treatment groups using the exact conditional test (ECT) version of the Mantel-Haenszel test to control for clustering by clinical center. For secondary efficacy outcomes, both cross-sectional descriptive statistics and changes from baseline were calculated. Changes over time are presented only for those with complete data at all follow-up visits.

Results

We recruited at a rate that was slower than expected, and with limited funding we closed the study prior to reaching the recruitment goal of 88 patients. A total of 81 patients were recruited between July 2008 and May 2009. The majority were white with a median age of 43 years (range 18 to 77 years). There were no statistically significant differences between the two treatment groups in demographic characteristics.

The two baseline symptom severity scores were averaged to provide an overall baseline score. Although the entry criteria only required a score of 3 or more on the 0-10 point severity scales for pain and frequency, 46% of subjects presented with severe pain (rating >7) and 56% with severe frequency (rating >7). Seventy-four percent of subjects self-reported at least 11 voids per day at both baseline visits. There were also no statistically significant differences in baseline symptoms between the groups.

Among the 81 randomized patients, 78 (96%) completed the 12 weeks of study. Three patients withdrew from the study during the first 12 weeks: 2 (5%) in the GTM group and 1 (3%) in the MPT group (see Figure 1). Two of the withdrawals had the primary reason for withdrawal as being “personal constraints”, and one as being “dissatisfied with treatment.” Among the 78 subjects who completed the study, 72 (92%) received at least seven of the ten assigned treatments; 21 (55%) of the subjects in MPT and 15 (38%) in GTM completed all ten assigned treatments in the 12 week study period. All subjects who withdrew from the study received fewer than 5 assigned treatments.

Overall, 59% in the MPT group and 26% in the GTM group reported moderate or marked improvement (p=0.0012) and were classified as ‘responders’ (Table 1). Interestingly, 43% in the GTM group reported no improvement, while the corresponding rate was only 18% in the MPT group.

Both treatment groups demonstrated improvement in secondary outcomes of pain, urgency, frequency, and quality of life (Table 2). While improvements tended to be greater in the MPT group, the differences were modest and none were statistically significantly different.

Overall, 62% (50/81) of participants reported at least one adverse event, classified as mild in 12% (10/81), moderate in 35% (28/81) or severe in 15% (12/81). The adverse event rate was 60% for GTM (25/42), as compared to 64% for MPT (25/39), with no statistically significant difference between treatment arms (p=0.73, exact ordered categorical test). The most common adverse event in both treatment groups was pain, primarily in the bladder or pelvis, reported by 14% of the participants. Pain was also the most common adverse event rated in the severe category; these reports mostly likely represent not only symptoms related to treatment but also the variable nature of the disorder. Less common adverse events were infection (12%), constitutional symptoms (11%), and gastrointestinal disturbances (10%). All other adverse events were infrequent. No serious adverse events (SAEs) were reported.

Unfortunately, there was considerable loss to follow-up during the 3-month period after the initial 12 weeks of treatment: after the follow-up phase of the study (during the three months after the initial 12 weeks of treatment), we had partial follow-up information on just 30 (77%) of the 39 patients assigned to MPT and on 28 (67%) of 42 assigned to GTM. Among

the 30 patients initially treated with MPT, 4 (13%) had elected to have continuing MPT during the 3 months follow-up period. Among the 28 patients initially treated with GTM, 8 (29%) had elected to have MPT treatment during the 3-month follow-up period. At the end of the follow-up phase, the final outcome of interest (GRA) was completed by just 11 of 42 (26%) in the GTM group and 23 of 39 (59%) in the MPT group. Therefore we are unable to draw any conclusions about the durability of treatment outcomes in either group.

Discussion

This study supports the concept of pelvic floor MPT for the treatment of IC/PBS, with nearly 60% of women experiencing moderate or marked improvement in overall symptoms compared to only 26% response in the active control group. While there were no statistically significant differences in symptom subscales of pain and QOL, change from baseline to week 12 in symptom severity and frequency favored MPT over GTM. These results support the findings from our pilot study,[9] and the results of other case series describing the results of manual therapies for relief of urologic pelvic pain conditions.[4,5] We feel these results justify clinical use of MPT in the treatment of IC/PBS and other pelvic pain conditions.

The etiology of the somatic abnormalities found in patients with urologic pain syndromes is not known. It is possible that the somatic abnormalities found in the lumbosacral dermatomyotomes in patients with IC/PBS are secondary, i.e. referred from a primary pelvic visceral abnormality. It is equally possible that these somatic abnormalities are a primary phenomenon and may themselves give rise to secondary visceral hypersensitivity. The latter possibility is supported by recent animal studies demonstrating induction of visceral (bladder) hypersensitivity by experimental injury to a somatic (sciatic) nerve that shares innervation with the viscus.[14]

Clinically, the somatic abnormalities associated with IC/PBS are obvious and have been recognized for some time.[1-8] It is appropriate that the role of the short, painful and/or hypertonic pelvic floor in the development of chronic genitourinary conditions has now begun to inform physiotherapeutic interventions aimed at rehabilitation;[15] whether the somatic abnormalities are primary or secondary, our studies suggest that it is clinically valuable to address and relieve them, as demonstrated here using specialized MPT.

The strengths of our study include its prospective, multicenter, randomized design with a standardized protocol for pelvic floor MPT and a positive control. Limitations include the fact that only 81 of the expected 88 women were enrolled, due to slow recruitment and loss of funding to complete the study. However, the study was still adequately powered to identify significant differences in the primary outcome of the study. The enrolled subjects also represent a select population drawn from academic medical centers, and recruitment was limited to subjects with pelvic floor tenderness on examination and a duration of symptoms less than three years. In addition, all subjects were treated by highly trained, experienced physical therapists, and we had a large number of patients who were ineligible for participation. Therefore the results may not be generalizable to the IC/PBS population at large, and we do not know whether MPT would benefit patients who have IC/PBS symptoms but who do not have pelvic floor tenderness. Nevertheless, the findings encourage further investigation of MPT as a treatment modality for IC/PBS, and suggest MPT could become a highly acceptable and clinically meaningful first-line therapy.

One important area for further study is the durability of responses to this therapy. Although the original design of this study including follow-up beyond the 12-week active treatment period, there was considerable loss to follow-up during the following 3-months. Therefore, we were unable to draw any conclusions about the durability of treatment outcomes in either

group. Some other important areas for further study include the need to determine the elements of an optimal MPT regimen, the duration of treatment necessary for durable response, the need for a clinical algorithm that is helpful in the identification of patients most likely to respond to treatment, and finally, the development and refinement of an optimal training program that can expand the population of physical therapists who can deliver effective pelvic floor MPT.

Appendix: ICCRN Membership

Acknowledgments

We thank the women who participated in this clinical trial. In addition to the authors, the Interstitial Cystitis Collaborative Research Network (ICCRN) Study Group includes the following institutions and individuals. The number of subjects randomized at each center is given in parentheses:

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University of Washington – Jane Miller, Charles H. Muller, Jean Kalhoff, James Bassuk, Sharon Downing, Robert F. Bale Jr.(9);

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University of Iowa – Michael O'Donnell, Susan Lutgendorf, Mary Eno, Kelly O'Berry (6);

Henry Ford Hospital – Kandis Rivers, Samina Romero, Michelle Peabody (6);

University of Rochester – Edward Messing, Elizabeth Betty Smith, Kay Rust, Jay Reeder (6);

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Abbreviations and Acronyms

CP	Chronic prostatitis
CPPS	Chronic pelvic pain syndrome
CPSI	Chronic Prostatitis Symptom Index
CTM	Connective Tissue Manipulation
GRA	Global Response Assessment
GTM	Global Therapeutic Massage

IC	Interstitial Cystitis
ICSI	O'Leary-Sant IC Symptom Index
ICPI	O'Leary-Sant IC Problem Index
PBS	Painful Bladder Syndrome
MPT	Myofascial Physical Therapy
NIH	National Institutes of Health
QOL	Quality of Life
UCPPS	Urologic Chronic Pelvic Pain Syndromes

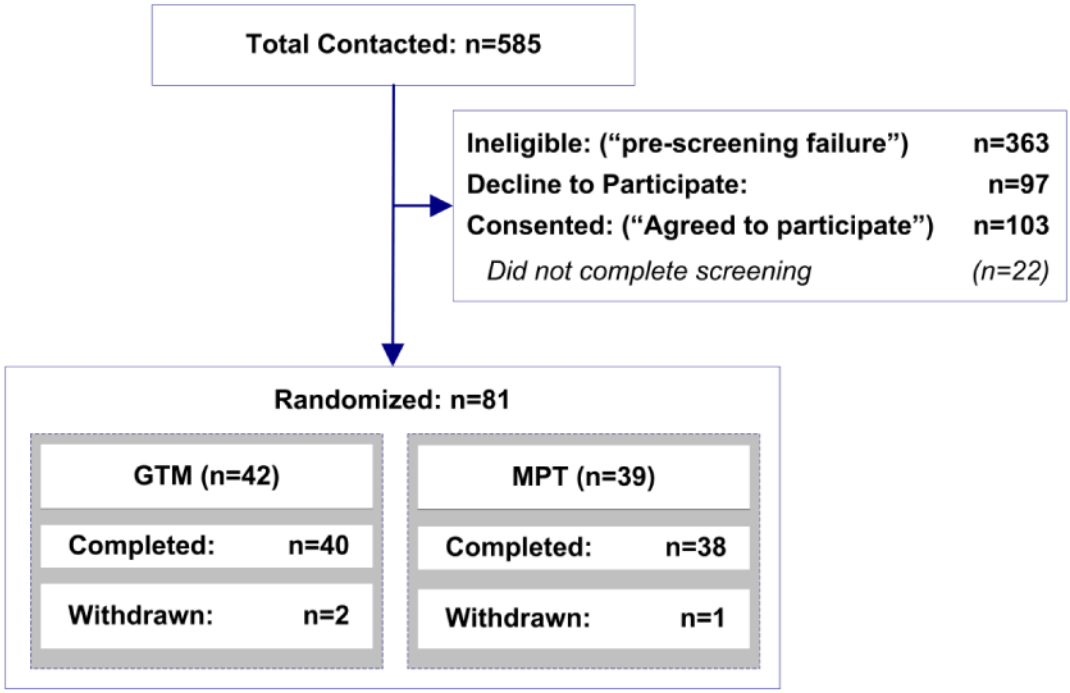

Figure 1.
Consort Diagram

Table 1

Primary Outcome: Global Response Assessment (GRA) after the 12-week treatment phase

	GTM	MPT	Total
Number of Subjects Randomized	42	39	81
Response Rate Based on GRA @ 12 wks. (p=0.0012)[1,2]			
Responders	11 (26.2%)	23 (59.0%)	34 (42.0%)
Non-responders	31 (73.8%)	16 (41.0%)	47 (58.0%)
Global Assessment of Response:			
Markedly Improved	5	10	15
Moderately Improved	6	13	19
Slightly Improved	13	9	22
No Change	14	5	19
Slightly Worsened	1	1	2
Moderately Worsened	0	0	0
Markedly Worsened	0	0	0
Missing or Withdrawn	3	1	4

[1]For the GRA portion of the response assessment, responders are defined as those reporting “Markedly Improved” or “Moderately Improved” on the GRA. Patients for whom the GRA value is missing are considered non-responders and included in the denominator for the assessment of response rates.

[2]Subjects who withdrew are included in the denominator.

Table 2

Secondary Outcomes: Means +/- Standard Deviations

Secondary Measures	Baseline		Week 12		Change from Baseline to week 12		Difference in change
	GTM (n=42)	MPT (n=39)	GTM (n=40)	MPT (n=38)	GTM (n=40)	MPT (n=38)	
Pain (0-10 Likert Scale)	5.8 +/- 1.7	6.1 +/- 1.7	4.3 +/- 2.3	3.8 +/- 2.3	-1.5 +/- 2.1	-2.2 +/- 2.2	p=0.27
Urgency (0-10 Likert Scale)	6.0 +/- 1.7	6.1 +/- 1.7	4.7 +/- 2.6	3.9 +/- 2.4	-1.4 +/- 2.6	-2.1 +/- 2.6	p=0.16
Frequency (0-10 Likert Scale)	6.2 +/- 1.7	6.5 +/- 1.8	4.9 +/- 2.4	4.3 +/- 2.4	-1.3 +/- 2.1	-2.2 +/- 2.3	p=0.17
24-hour frequency (urinary diary)	12.4 +/- 4.8	13.6 +/- 6.3	11.1 +/- 4.5	11.6 +/- 4.8	-1.3 +/- 3.6	-2.0 +/- 3.7	p=0.49
ICSI (max range 0-20)	11.4 +/- 3.5	11.9 +/- 3.4	9.3 +/- 4.4	8.6 +/- 4.2	-2.2 +/- 3.2	-3.2 +/- 3.7	p=0.31
ICPI (max range 0-16)	10.7 +/- 3.0	10.5 +/- 2.8	8.3 +/- 3.7	6.9 +/- 3.4	-2.4 +/- 2.6	-3.6 +/- 3.6	p=0.09
SF12 PCS (max range 0-100)*	45.4 +/- 10.0	41.5 +/- 10.0	46.0 +/- 10.5	45.6 +/- 9.4	0.3 +/- 6.9	4.1 +/- 9.2	p=0.08
SF12 MCS (max range 0-100)*	45.8 +/- 8.8	40.1 +/- 8.9	49.3 +/- 8.5	45.0 +/- 10.8	3.5 +/- 7.5	5.2 +/- 11.0	p=0.86
FSFI (range)	20.7 +/- 7.9	18.7 +/- 8.2	22.2 +/- 8.7	20.5 +/- 8.5	2.3 +/- 7.5	2.0 +/- 5.6	p=0.67
FSQ (max range 0-43)[1]	28.1 +/- 6.9	29.8 +/- 6.0	22.4 +/- 9.6	21.1 +/- 9.5	-5.9 +/- 7.9	-8.9 +/- 9.1	p=0.22

[1]Note that for the two composite measures of the SF-12, as well as the FSFI, higher values represent better functioning. Thus, positive changes from baseline represent improvement.

Table A
Summary of Demographic Characteristics by Treatment Group

	GTM	MPT	Total
Number of Subjects	42	39	81
Age (p=0.98)			
Mean ± s.d.	43.0 +/- 12.9	43.1 +/- 15.1	43.0 +/- 13.9
Median	43.0	40.0	42.0
Range	24 to 71	18 to 77	18 to 77
Race (p^4=0.06)			
Asian/Asian-American	0 (0%)	1 (3%)	1 (1%)
Black/African-American	3 (7%)	1 (3%)	4 (5%)
White/Caucasian	38 (90%)	30 (77%)	68 (84%)
Multi-race	0	1 (3%)	1 (1%)
Other	0	6 (15%)	6 (7%)
Missing	1	0	1
Educational Level (p=0.17)			
Less than High school	0	0	0
High School/GED	5 (12%)	9 (24%)	14 (18%)
Some college	11 (26%)	10 (26%)	21 (26%)
Graduated college or above	26 (62%)	19 (50%)	45 (56%)
Missing	0	1	1
Employment (p=0.75)			
Employed	29 (69%)	23 (59%)	52 (64%)
Unemployed/Retired	8 (19%)	11 (28%)	19 (23%)
Fulltime Homemaker	3 (7%)	2 (5%)	5 (6%)
Disabled	2 (5%)	3 (8%)	5 (6%)
Annual Family Income (p=0.91)			
<$10,000	2 (6%)	2 (6%)	4 (6%)
$10,001 - $25,000	0	2 (6%)	2 (3%)
$25,001 - $50,000	8 (25%)	10 (31%)	18 (28%)
$50,001 - $100,000	15 (47%)	6 (19%)	21 (33%)
>$100,000	7 (22%)	12 (38%)	19 (30%)
Missing	10	7	18

[4] p-value is from a test for white versus non-white.

Table B
Baseline Symptoms by Treatment Group

	GTM	MPT	Total
Number of Subjects	42	39	81
Average Pain Severity Score (p^5=0.42)			
None (0)	0	0	0
Mild (1-3)	3 (7%)	1 (3%)	4 (5%)
Moderate (4-6)	21 (50%)	19 (49%)	40 (49%)
Severe (7-10)	18 (43%)	19 (49%)	37 (46%)
Average Urgency Severity Score (p^1=0.58)			
None (0)	0	0	0
Mild (1-3)	3 (7%)	3 (8%)	6 (7%)
Moderate (4-6)	22 (52%)	17 (44%)	39 (48%)
Severe (7-10)	17 (40%)	19 (49%)	36 (44%)
Average Frequency Severity Score (p^1=0.40)			
None (0)	0	0	0
Mild (1-3)	2 (5%)	2 (5%)	4 (5%)
Moderate (4-6)	19 (45%)	13 (33%)	32 (40%)
Severe (7-10)	21 (50%)	24 (62%)	45 (56%)
Patient-Reported 24-hour Frequency (p^6=0.52)			
<6 times at both visits	1 (2%)	0 (0%)	1 (1%)
<6 times, 7-10 times	2 (5%)	1 (3%)	3 (4%)
7-10 times at both visits	10 (24%)	8 (21%)	18 (22%)
7-10 times, 11-14 times	8 (19%)	6 (15%)	14 (17%)
7-10 times, 15+ times	1 (2%)	0 (0%)	1 (1%)
11-14 times at both visits	11 (26%)	13 (33%)	24 (30%)
11-14 times, 15+ times	2 (5%)	2 (5%)	4 (5%)
15+ times at both visits	7 (17%)	9 (23%)	16 (20%)

[5]The p-value was based on a Cochran-Mantel-Haenszel test.

[6]The p-value was based on only the baseline Visit 2 data. At that visit, 2 (2%) reported 24-hour frequency <6 times, 25 (31%) 7-10 times, 36 (44%) 11-14 times, and 18 (22%) 15 times or greater.