Randomized Multicenter Feasibility Trial of Myofascial Physical Therapy for the Treatment of Urological Chronic Pelvic Pain Syndromes

Mary P. FitzGerald,* Rodney U. Anderson,† Jeannette Potts,‡ Christopher K. Payne, Kenneth M. Peters,§ J. Quentin Clemens,‖,¶ Rhonda Kotarinos, Laura Fraser, Annemarie Cosby, Carole Fortman, Cynthia Neville, Suzanne Badillo, Lisa Odabachian, Andrea Sanfield, Betsy O'Dougherty, Rick Halle-Podell, Liyi Cen, Shannon Chuai, J. Richard Landis,** Keith Mickelberg, Ted Barrell, John W. Kusek and Leroy M. Nyberg for the Urological Pelvic Pain Collaborative Research Network

From the Loyola University Medical Center, Maywood (MPF, RK, CF), Massage Therapy of Oak Park, Oak Park (RHP), Rehabilitation Institute of Chicago, Chicago (CN, SB), Illinois, Stanford University School of Medicine, Stanford, California (RUA, CKP, LF, AC), Cleveland Clinic Foundation, Cleveland, Ohio (JP, BO), William Beaumont Hospital, Royal Oak (KMP, LO, AS) and The University of Michigan Medical Center, Ann Arbor (JQC), Michigan, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania (LC, SC, JRL, KM, TB), and National Institutes of Health, Bethesda, Maryland (JWK, LMN)

Abbreviations and Acronyms

AE = adverse event
CP = chronic prostatitis
CPPS = chronic pelvic pain syndrome
CPSI = Chronic Prostatitis Symptom Index
CTM = connective tissue manipulation
FSFI = Female Sexual Function Index
GRA = global response assessment
GTM = global therapeutic massage
IC = interstitial cystitis
ICPI = O'Leary-Sant IC Problem Index
ICSI = O'Leary-Sant IC Symptom Index
MPT = myofascial physical therapy
NIH = National Institutes of Health
PBS = painful bladder syndrome
QOL = quality of life
SF-12 = 12-Item Short-Form Health Survey
UCPPS = urological chronic pelvic pain syndromes
UPPCRN = Urological Pelvic Pain Collaborative Research Network

Purpose: We determined the feasibility of conducting a randomized clinical trial designed to compare 2 methods of manual therapy (myofascial physical therapy and global therapeutic massage) in patients with urological chronic pelvic pain syndromes.

Materials and Methods: We recruited 48 subjects with chronic prostatitis/chronic pelvic pain syndrome or interstitial cystitis/painful bladder syndrome at 6 clinical centers. Eligible patients were randomized to myofascial physical therapy or global therapeutic massage and were scheduled to receive up to 10 weekly treatments of 1 hour each. Criteria to assess feasibility included adherence of therapists to prescribed therapeutic protocol as determined by records of treatment, adverse events during study treatment and rate of response to therapy as assessed by the patient global response assessment. Primary outcome analysis compared response rates between treatment arms using Mantel-Haenszel methods.

Results: There were 23 (49%) men and 24 (51%) women randomized during a 6-month period. Of the patients 24 (51%) were randomized to global therapeutic massage, 23 (49%) to myofascial physical therapy and 44 (94%) completed the study. Therapist adherence to the treatment protocols was excellent. The global response assessment response rate of 57% in the myofascial physical therapy group was significantly higher than the rate of 21% in the global therapeutic massage treatment group ($p = 0.03$).

Submitted for publication December 22, 2008.
Study received institutional review board approval.
Clinical Trial Registration NCT00434343 (www.clinicaltrials.gov).
* Correspondence: Loyola University Medical Center, Bldg 103, Room 1004, Maywood, Illinois 60153 (telephone: 708-216-2170; FAX: 708-216-2171; e-mail: mfitzg8@lumc.edu).
† Financial interest and/or other relationship with Astellas, GSK, Boston Scientific and Bioness Inc.
‡ Financial interest and/or other relationship with Pfizer.
§ Financial interest and/or other relationship with Medtronic, Boston Scientific, Indevus, Allergan, Pfizer and Trillium Therapeutics.
‖ Conducted this research while at Northwestern University.
¶ Financial interest and/or other relationship with Merck, Pfizer, Medtronic and Tengion.
** Financial interest and/or other relationship with Bristol-Myers Squibb and Sanofi-Aventis.

See Editorial on page 427.

0022-5347/09/1822-0570/0
THE JOURNAL OF UROLOGY®

Vol. 182, 570-580, August 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2009.04.022

Conclusions: We judged the feasibility of conducting a full-scale trial of physical therapy methods and the preliminary findings of a beneficial effect of myofascial physical therapy warrants further study.

Key Words: prostatitis; cystitis, interstitial; physical therapy modalities

THE urological chronic pelvic pain syndromes, which include interstitial cystitis/painful bladder syndrome in men and women, and chronic prostatitis/chronic pelvic pain syndrome in men, are characterized by pelvic pain with concurrent urinary symptoms. PBS, as defined by the International Continence Society, is "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology."[1] These symptoms may be related to interstitial cystitis, with additional characteristic findings of glomerulations and/or ulcers present at cystoscopy, and hydrodistention.[2] The underlying pathophysiology of these disorders has not been elucidated, and the relationship between PBS and IC is not clear.

Chronic prostatitis/chronic pelvic pain syndrome or NIH type IIIA/IIIB prostatitis is also characterized by pelvic pain and lower urinary tract symptoms in the absence of proven urinary tract infection or other obvious disease pathology. CP/CPPS is also a clinical description based on symptoms and does not depend on urodynamic or cystoscopic findings.

Estimates of the national prevalence of these UCPPS vary widely according to the populations studied and the survey methodology. In 1990 interstitial cystitis was thought to affect as many as 500,000 United States citizens with 25% of patients younger than 25 years.[3] Recent estimates vary between 0.2% and 3.4% of the population.[4–9] In 2000 annual national expenditures in the United States for IC/PBS were estimated at $797 million.[10] Estimates of the prevalence of symptoms characteristic of CP/CPPS vary similarly and may be higher, with community based surveys demonstrating a prevalence of 8% to 11.5% in men younger than 50 years.[11,12]

On examination, tension and tenderness of the pelvic floor musculature and other somatic tissues are commonly present in patients with UCPPS.[13–20] It is thought that these myofascial abnormalities contribute significantly to the pain of UCPPS. However, it is not known whether these musculoskeletal abnormalities are a consequence of lower urinary tract symptoms or are a primary disorder which gives rise to secondary urinary symptoms. Frequently found abnormalities include myofascial trigger points defined as taut bands or tender nodules that evoke twitch responses or reproduce the character and location of symptoms during careful palpation.[21] Importantly there have been several reports of UCPPS symptom relief by therapeutic efforts directed at those muscular abnormalities.[16–20] In practice those therapeutic interventions are typically performed by a physical therapist skilled in manual therapy techniques. Although widely practiced, to our knowledge no randomized trials have established the effectiveness of specialized external and pelvic floor physical therapy for UCPPS.

Since there have been few prospective randomized clinical trials involving physical therapies to guide us, we designed a study to determine whether a randomized study of physical therapy for treatment of UCPPS is feasible. The criteria to assess feasibility were whether patients with UCPPS are willing to be randomized between 2 forms of manual physical therapy, whether physicians are capable of identifying relevant myofascial abnormalities during evaluation of patients with UCPPS, whether we can assure that the manual therapy treatments are similar in nature and quality at several study sites, and whether we can assess the safety of manual therapies for UCPPS and determine the response rate to manual physical therapy.

METHODS

The Urological Pelvic Pain Collaborative Research Network is a cooperative network of investigators from 20 clinical centers and a Data Coordinating Center funded by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (http://www.cceb.med.upenn.edu/uppcrn) (Appendix 1). The study received institutional review board approval at all enrolling sites and the Data Coordinating Center located at the University of Pennsylvania School of Medicine. The UPPCRN Data and Safety Monitoring Board oversaw aspects of clinical trial design, conduct and analyses of trial data.

Study Design

This was a randomized, single-blind clinical trial in which 8 participants each were to be recruited by a subset of 6 of the UPPCRN clinical centers for a total sample size of 48. Subjects who met eligibility criteria and did not have any of the exclusion factors were randomized in equal number to MPT or GTM and were not informed whether the treatment they were receiving was MPT or GTM (Appendix 2). MPT treatment targeted internal (pelvic) and external trigger point work, focusing on the muscles and connective tissues of the pelvic floor, hip girdle and abdomen,

whereas GTM was considered a nonspecific somatic treatment with full-body Western massage and was included as a comparison treatment arm. Patients were scheduled for 10 weekly treatments of 1 hour each. Participation ended when a subject completed treatment and outcome assessment, voluntarily withdrew or was withdrawn by their physician for medical reasons.

Study Measures

Since this was a pilot study to establish the feasibility of comparing 2 manual therapies, many of the trial outcomes were related to study conduct. These measures included 1) the proportion of patients who consented to join the study from among all eligible patients approached, 2) the number of patients deemed eligible by physicians based on history and clinical examination, and the number considered ineligible by physical therapists due to lack of relevant physical abnormalities, and 3) adherence of therapist to prescribed therapeutic protocol as determined by records of treatment.

The primary measures related to patient outcomes including safety and efficacy were 1) adverse events including serious adverse events, 2) patient global response assessment with patients classified as responders if they stated that symptoms were moderately or markedly improved compared to how they were before treatment (Appendix 3) and 3) change in several validated symptom scales.

Eligibility Assessment

Recruitment was conducted from among patients who attended urology and urogynecology clinics at each of the designated clinical sites based on the inclusion and exclusion criteria outlined in Appendix 2. Potential participants had to be adult and have a clinical diagnosis of IC/PBS or CP/CPPS. Based on personal experience the investigators hypothesized that the time to response to physical therapies is proportional to the duration of symptoms. Since treatment was limited to 10 sessions in this protocol we restricted entry to subjects with symptoms present for less than 3 years. The patient must have previously undergone at least 1 course of another form of therapy for his/her symptoms. We also excluded patients who were intolerant to digital vaginal or rectal examination, ie unable to tolerate the MPT treatments. Participants who had previously undergone myofascial physical therapy for symptoms were also ineligible.

Certification of Treating Therapists

Certification of treating therapists took place in several steps. Up to 2 physical therapists were involved at each clinical site. As a prerequisite the licensed physical therapists and collaborating investigator physicians attested that they already routinely treated patients with UCPPS using MPT techniques similar to those used in the study. To standardize MPT and GTM treatments therapists received study materials including the study protocol, description of the MPT and GTM treatments, and DVDs demonstrating MPT and GTM therapies. They attended a weekend certification session during which the study protocol and treatments were reviewed and demonstrated on volunteers. A licensed massage therapist (RH-P) instructed therapists in the proper performance of a traditional Western style massage.[22] For preliminary certification candidate therapists demonstrated full understanding and competence in the execution of the steps involved in completion of MPT and GTM treatments. After subsequently completing and attesting to correct performance of 5 treatments of each type, therapists were then certified to participate in the protocol.

Preintervention Assessments

Clinically identified potential participants were counseled about study procedures and were administered informed consent. During the first study visit patients completed symptom scales including a rating of average pelvic/bladder discomfort or pain, and of urinary urgency and urinary frequency severity, all rated on average in the last 4 weeks. Other symptom scales included the IC Symptom and Problem Index,[23] NIH-CPSI (males),[24] SF-12 Health Status Questionnaire[25] and a gender specific sexual function index (FSFI[26] or Sexual Health Inventory for Men[27]). Patients also underwent pelvic examination by the study physician including transvaginal or transrectal examination of the soft tissues of the pelvic floor (levator ani, obturator internus and tissues of the urogenital diaphragm). Patients were eligible to continue with study participation if some pelvic floor tenderness was elicited in any of the designated areas during this baseline pelvic examination. Patients without such tenderness were excluded from further participation.

At the second study visit patients underwent a more complete examination of the musculoskeletal system and soft tissues by the study physical therapist. Patients were eligible to continue participation in the study only if the therapist confirmed that there was tenderness present on pelvic examination. The location of the tenderness did not have to correspond to that found by the primary investigator. Other pretreatment assessments by the physical therapist included mapping of any scars and connective tissue restrictions, and evaluation of all soft tissues of the back, hip girdle, abdominal wall and pelvic floor.

Participants meeting all eligibility criteria were randomly assigned in equal proportions within each of the 6 strata defined by clinical site via a prespecified sequence distributed in a series of sealed envelopes to receive MPT or GTM. Each participant underwent 10 weekly 1-hour treatments by the physical therapist. Patients were contacted by telephone by the study coordinator every week between treatments and asked about any adverse events. Study coordinators remained masked to study treatment assignment.

MPT Treatment

Patients randomized to the MPT group underwent connective tissue manipulation to all body wall tissues of the abdominal wall, back, buttocks and thighs that clinically were found to contain connective tissue abnormalities and/or myofascial trigger point release to painful myofascial trigger points. CTM was applied bilaterally to the patient in the prone position, posteriorly from inferior thoracic level 10 to the popliteal crease. This was done

until a texture change was noted in the treated tissue layer. Manual techniques such as trigger point barrier release with or without active contraction or reciprocal inhibition, manual stretching of the trigger point region and myofascial release were used on the identified trigger points.

Once adequate changes were noted in the posterior tissues the patient was repositioned into the supine position for CTM to bilateral anterior tissues. This allowed the inclusion of the thighs, laterally, anteriorly and medially from the knee up to and including the thigh crease. CTM was performed on the abdominal wall from the suprapubic rim to the anterior costal cartilages, with a concentration of manual interventions to focus on the periumbilical tissues. Manual trigger point release techniques were used to treat any noted trigger points or scars in the anterior or posterior lower quadrants. It was presumed that external episiotomy scars found in the perineum or external pelvic floor were especially relevant.

Transvaginal/transrectal treatment of the soft tissues of the pelvic floor with CTM of periurethral tissues, arcus tendineus fascia pelvis, muscle origins and insertions was also performed. Myofascial manipulation to each muscle group was performed with the focus on restrictive bands and trigger points. Neuromuscular reeducation, focusing on lengthening the pelvic floor musculature, was performed in conjunction with myofascial manipulation including post-isometric relaxation.

During the time between visits, when deemed appropriate by the therapist, patients were asked to double void 2 to 3 times after each void (ie after voiding, to remain seated on the toilet and to relax or drop the pelvic floor again as if to initiate voiding). This was meant to facilitate a proprioceptive awareness of the movement of the pelvic floor during voiding, hoping to use recent recall to make dropping the pelvic floor easier. As their ability to drop the pelvic floor improved the patients could add 5 pelvic drops to the end of the exercise. Squatting was also taught as a position to use to facilitate and practice pelvic floor drops.

The treating physical therapist was permitted to vary the exact content of the hour-long MPT treatment based on the physical abnormalities present and on the response of tissues to manipulation. Initial treatments devoted at least half of the treatment time to external myofascial therapy. As connective tissue changes became evident with repetitive treatments, less time was typically needed for treatment of external tissues and more time was devoted to internal (transvaginal, transrectal) work. When the severity of symptoms prohibited transvaginal/transrectal myofascial trigger point release or CTM (although initial examination and inclusion of the patient was possible) this variance was allowed.

To maximize the potential for a treatment effect each therapist typically offered appropriate home exercises to each patient randomized to the MPT arm. Each therapist was provided with a catalog of stretches and/or exercises specifically chosen for this study and the appropriate exercise/stretch was given to the patient when desired by the therapist. Importantly these were not Kegel exercises which can increase the irritability of myofascial trigger points and exacerbate symptoms if practiced during an early phase of therapy. Later after muscle control is achieved a focus on improving muscle strength may be more appropriate and was permitted by the protocol.

GTM Treatment

Patients randomized to the GTM group received weekly massages consisting of full body Western massage for 1 hour. Unlike the MPT arm in which the therapists tailored the focus of therapy to target individual patient needs, GTM was used according to a common study protocol. This differs from clinically practiced therapeutic massage as the participating therapists were neither permitted to deviate from the GTM regimen nor to tailor the massage techniques to individual patients. Techniques used include effleurage, petrissage, friction, tapotement, vibration and kneading. These techniques were applied in upper and lower limbs, trunk, buttocks, abdomen, head and neck each for prescribed time periods (eg 10 minutes massage to head and neck). Patients randomized to GTM were not provided with a home exercise program. The GTM treatment was not similar to the MPT treatment with respect to the manual methods administered to the body tissues, ie there was no methodological overlap between treatments.

Statistical Analysis

To ensure balance across treatment arms a stratified randomization was used. Within each of the 6 strata defined by clinical site subjects were further stratified by gender and randomly allocated in equal proportions to the 2 treatment arms.

Although this was a pilot study for which comparison of treatment efficacy was a secondary outcome, the small number of participants (24 per arm) was adequate to provide approximately 80% power to detect a 40% absolute difference (eg 70% vs 30%) in response rates between MPT and GTM using a 2-sided test at the 5% level. With a total of 24 subjects per treatment arm 95% confidence intervals for rates (such as response and adverse events) have a maximum width of $\pm 20\%$, ignoring slight adjustments for variability due to clinical site.

An intent to treat analysis including all randomized participants was implemented. Participants who discontinued treatment during the trial, particularly in the case of an adverse event, were not considered withdrawals from study unless they withdrew consent for further followup. However, randomized participants who withdrew before the final assessment at 12 weeks were considered to represent treatment failures and were included in the denominator for evaluation of response rates based on the GRA.

The primary efficacy end point was response rate based on the GRA (Appendix 3). An analysis comparing response rates between treatment arms using the exact conditional test version of Mantel-Haenszel methods to adjust for within-center clustering was implemented within the Proc-StatXact software system.[28] Outcome measures between treatment arms were analyzed with Wilcoxon rank sum tests, and outcome scores within treatment groups and disease states were determined with paired t tests. Statistical significance was at $p < 0.05$.

RESULTS

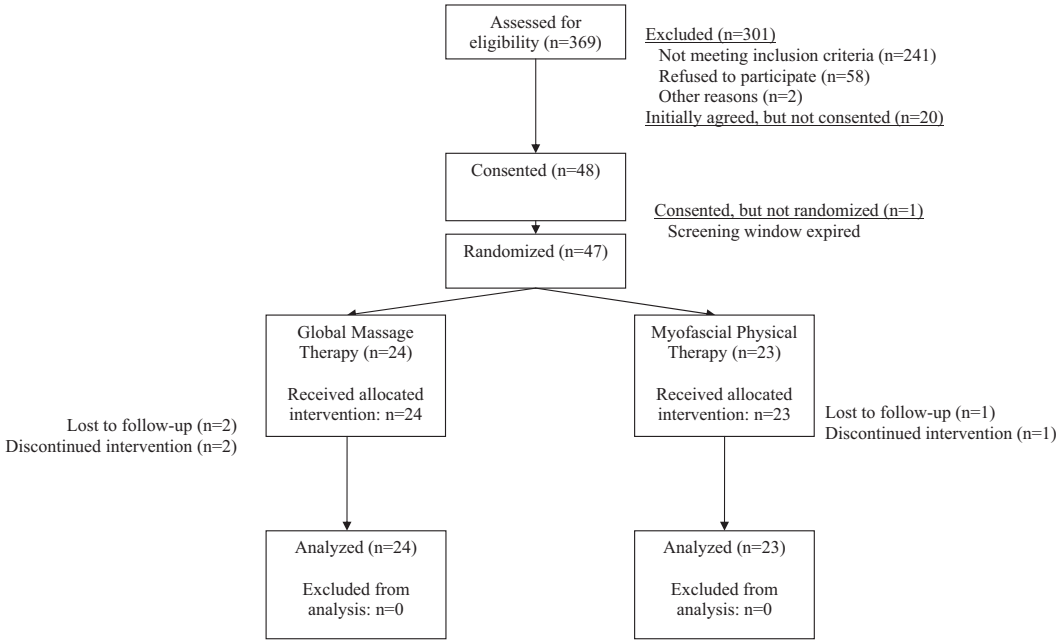
As detailed in the figure 369 patients with UCPPS were reviewed for study participation, of whom 68 (18%) agreed to participate and 47 were randomized, including 23 (49%) men and 24 (51%) women. Recruitment took place during 6 months. All except 1 patient identified as eligible by the study physician were also considered eligible by the study physical therapist on the basis of the presence of tenderness of the pelvic floor. There were 24 (51%) patients randomized to GTM and 23 (49%) to MPT. Patients with IC/PBS included 24 women and 2 men, and 21 men had a CP/CPPS diagnosis. A total of 44 (94%) patients completed the study, with 2 withdrawing from the GTM treatment arm and 1 withdrawing from MPT.

The baseline demographic characteristics of study participants overall and by treatment assignment are presented in table 1. Mean age was 43 years (range 22 to 76) and 41 participants (87%) were white. Patient self-reports of medical history differed between the 2 disorders with a higher incidence of migraine headaches, GI disorders, drug allergies and sinusitis in those with IC/PBS ($p < 0.05$). Patient symptoms before treatment were rated moderate to severe (range 4 to 10 on a scale of 10) for pain in 96%, urgency in 91% and frequency in 89% of participants (table 2).

The median (range) number of treatment visits administered in the MPT group was 10 (4 to 10) and in the GTM group was 10 (1 to 10). Of the patients 87% in each arm received at least 7 of the assigned treatments. Therapist adherence to the treatment protocols was excellent. During GTM treatments therapists recorded having performed massage to all body parts during all treatments as prescribed by the protocol except for omission of head and neck and/or abdominal massage during most treatments in 1 patient (protocol violation). Therapists reported they applied all of the allowed therapeutic interventions at least some of the time and varied treatments as allowed by the protocol. The most commonly used interventions were connective tissue manipulation of external tissues of lower limbs, buttocks, abdominal wall and pelvic floor as well as trigger point treatments to the abdominal wall and pelvic floor. Individualized home stretch/exercise programs were prescribed for 21 (48%) patients, of which 1 patient performed none, 5 performed some and 15 performed all. After treatment 42 of 44 (95%) patients correctly identified the study group to which they were assigned.

Adverse events were reported by 5 (21%) patients in the GTM group and 12 (52%) patients in the MPT group (table 3). Pain was the most common class of AEs as reported by 14 (30%) participants, of which 3 pain AEs were rated as severe (1 in GTM group and 2 in MPT group).

The overall GRA response rates and rates for subgroups of subjects with IC/PBS and CP/CPPS are shown in table 4. The overall GRA response rate of 57% in the MPT group was significantly higher than the rate of 21% in the GTM treatment group ($p = 0.03$). As detailed in table 4 a significant



CONSORT diagram (Consolidated Standards of Reporting Trials)

Table 1. *Summary of demographic characteristics*

	Treatment						p Value
	GTM		MPT		Overall		
No. subjects	24		23		47		
No. gender (%):							0.66
M	11	(46)	12	(52)	23	(49)	
F	13	(54)	11	(48)	24	(51)	
Age:							0.28
Mean ± SD	44.9 ± 14.0		41.1 ± 11.4		43.0 ± 12.8		
Median (range)	45.1 (22–76)		40.9 (23–66)		43.3 (22–76)		
No. ethnicity/race (%):							0.42 (white vs nonwhite)
North American Indian/ North Native	0		0		0		
Asian/Asian-American	0		1	(4)	1	(2)	
Black/African-American	0		2	(8)	2	(4)	
White/caucasian	22	(92)	19	(83)	41	(87)	
Native Hawaiian/other Pacific Islander	0		0		0		
Other	2	(8)	1	(4)	3	(6)	
No. diagnosis (%):							0.67
IC/PBS	14	(58)	12	(52)	26	(55)	
CP/CPPS	10	(42)	11	(48)	21	(45)	
No. educational level (%):							0.13
Less than high school	0		0		0		
High school/GED	5	(21)	1	(5)	6	(13)	
Some college	7	(29)	7	(30)	14	(30)	
Graduated college or greater	12	(50)	15	(65)	27	(57)	
No. employment (%):							0.15
Employed	14	(58)	17	(74)	31	(66)	
Unemployed/retired	7	(29)	2	(9)	9	(19)	
Full-time homemaker	3	(13)	2	(9)	5	(11)	
Disabled	0	(0)	2	(9)	2	(4)	
No. annual family income (%):							0.89
Less than $10,000	1	(7)	1	(7)	2	(7)	
$10,001–$25,000	1	(7)	0	(0)	1	(3)	
$25,001–$50,000	3	(20)	4	(29)	7	(24)	
$50,001–$100,000	4	(27)	3	(21)	7	(24)	
Greater than $100,000	6	(40)	6	(43)	12	(41)	
Missing	9		9		18		

Treatment groups were similar with respect to all demographic characteristics at baseline. All but 2 patients in the IC/PBS group were female.

difference between treatment arms was present in the IC/PBS group but not in the CP/CPPS group since many patients with CP/CPPS responded to GTM and MPT.

Tables 5 and 6 show baseline and 12-week symptom scores according to clinical diagnosis of IC/PBS and CP/CPPS, respectively, stratified by treatment assignment. MPT resulted in improved (decreased) symptom scores for patients with IC/PBS and CP/CPPS (table 5, $p < 0.05$). GTM did not provide any significant relief of symptom scores for the IC/PBS group, but was associated with improvements in the CP/CPPS group in domains of pain, quality of life and ICSI (table 6, $p < 0.05$). The SF-12 physical and mental component scores in both disorder groups were unaffected by GTM. Sexual function improved with MPT for the IC/PBS group, but not CP/CPPS.

Physician baseline physical examination of internal muscle tenderness/pain to palpation across left and right side within each muscle group (total score for each muscle group range 0 to 6) resulted in an average total score of 10.96 across the 4 muscle groups, significantly less than the average assessment of 17.78 at baseline ($p < 0.001$). Table 7 presents the level of tenderness/pain to palpation by disorder and treatment arm at baseline and at the final 12-week physician evaluation for each of the 4 muscle groups. MPT resulted in significant relief of tenderness/pain of the internal muscle groups in the patients with IC/PBS compared with GTM ($p < 0.05$). The painful tender points in patients with CP/CPPS were relieved by MPT. However, some muscle groups (anterior and posterior levator) were similarly relieved after GTM. Minimal urogenital diaphragm tenderness did not change with either therapeutic approach.

DISCUSSION

To our knowledge this is the first published randomized trial comparing MPT and GTM for UCPPS treatment. We achieved our objective of demonstrating that such a clinical trial was feasible. Patients were willing to be randomized between 2 forms of manual treatment, with 38% (48 of 128) of those screened and found to be eligible for study inclusion agreeing to be randomized. We were also able to standardize both treatment approaches with reports of almost complete adherence to prescribed patterns

Table 2. *Baseline symptom characteristics by treatment group at baseline*

	No. GTM (%)	No. MPT (%)	No. Total (%)	p Value*
Av pain severity score:				0.17
None (0)	0 (0)	0 (0)	0 (0)	
Mild (1–3)	2 (8)	0 (0)	2 (4)	
Moderate (4–6)	11 (46)	9 (39)	20 (43)	
Severe (7–10)	11 (46)	14 (61)	25 (53)	
Av urgency severity score:				0.15
None (0)	0 (0)	0 (0)	0 (0)	
Mild (1–3)	4 (17)	0 (0)	4 (9)	
Moderate (4–6)	8 (33)	9 (39)	17 (36)	
Severe (7–10)	12 (50)	14 (61)	26 (55)	
Av frequency severity score:				0.16
None (0)	0 (0)	0 (0)	0 (0)	
Mild (1–3)	4 (17)	1 (4)	5 (11)	
Moderate (4–6)	6 (25)	5 (22)	11 (23)	
Severe (7–10)	14 (58)	17 (74)	31 (66)	

Pain, urgency and frequency values represent means of scores at baseline visits 1 and 2. Treatment groups were similar at baseline with respect to symptom severity.

* Corresponds to test comparing scores by treatment group.

Table 3. *Cumulative adverse events by body system and treatment arm*

	No. GTM Toxicity Grade					No. MPT Toxicity Grade				
	None (grade 0)	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3)	Total (%)	None (grade 0)	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3)	Total (%)
Highest AE grade	19	3	1	1	5 (21)	11	8	2	2	12 (52)
Cardiovascular (arrhythmia)	24	0	0	0	0	22	0	1	0	1 (4)
Constitutional symptoms	22	2	0	0	2 (8)	22	1	0	0	1 (4)
Hemorrhage	24	0	0	0	0	22	1	0	0	1 (4)
Infection	23	0	1	0	1 (4)	23	0	0	0	0
Musculoskeletal	24	0	0	0	0	22	1	0	0	1 (4)
Pain (unspecified):	21	1	1	1	3 (13)	12	8	1	2	11 (48)
Abdomen/intestine							1	1	0	
Back		0	1	0			1	0	0	
Bladder/rectum/pelvis/genital		1	2	1			5	1	2	
Genitourinary	23	1	0	0	1 (4)	19	4	0	0	4 (17)

Body systems were not included if no related AEs were reported. All adverse events included, regardless of relationship to study intervention. Patients were counted once in each category and included in the column relating to their worst toxicity grade. Patients may have had events in more than 1 body system category. An adverse event was not counted if the same event was observed at baseline with an equal or greater toxicity grade.

for GTM and reports of appropriate, tailored myofascial physical therapy applied to patients in the MPT group. All AEs were more common in the MPT group as expected but our low study withdrawal rate and low rate of severe adverse events suggest that patients found the study treatments highly acceptable. Finally the overall response rate of 57% in the MPT group suggests that MPT represents a clinically meaningful treatment option, supporting the findings of others.[16–20]

Table 4. *Global response assessment by treatment group*

	No. GTM	MPT	Total	p Value
No. response rate based on GRA (%):*				0.03
Responders	5 (21)	13 (57)	18 (38)	
Nonresponders	19 (79)	10 (43)	29 (62)	
No. response rate for IC/PBS subgroup (26) (%):				0.03
Responders	1 (7)	6 (50)	7 (27)	
Nonresponders	13 (93)	6 (50)	19 (73)	
No. response rate for CP/CPPS subgroup (21) (%):				0.39
Responders	4 (40)	7 (64)	11 (52)	
Nonresponders	6 (60)	4 (36)	10 (48)	
No. global assessment of response:				
Markedly improved	3	8	11	
Moderately improved	2	5	7	
Slightly improved	10	6	16	
No change	5	2	7	
Slightly worsened	1	0	1	
Moderately worsened	1	1	2	
Markedly worsened	0	0	0	
Missing or withdrawn	2	1	3	

* 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 are included in the denominator for the assessment of response rates. Subjects who withdrew from the study are also included in the denominator.

A feasibility study was necessary as there was some skepticism regarding patient willingness to be randomized between 2 forms of manual therapy for UCPPS. Myofascial physical therapy can be painful and/or seem unduly invasive. In addition, UPPCRN sites are regional referral centers, and patients often expect immediate resolution of symptoms and may be unwilling to risk randomization to treatment with an unproven therapy. Study participation can be further challenged by the logistical obstacles of time and distance in such referral patients as this was a demanding treatment protocol that required multiple treatment visits.

We made several interesting observations. There was a striking difference in the response rate on the GTM arm between success rates in CP/CPPS (all men) and IC/PBS (all but 2 of whom were women) at 40% in CP/CPPS and 7% in IC/PBS. This suggests that CP/CPPS responds differently to GTM or that men respond differently to GTM, or that other unmeasured factors are important. Since all the study therapists were women, male patients might have responded to receiving nonsexual therapeutic touch administered by a woman. This hypothesis could be tested, for example, by studying similar therapies administered to men by male therapists. At a minimum these results suggest that therapeutic massage may merit further study as a therapeutic alternative for UCPPS.

There were a number of strengths of our study. The standardization of treatment arms was across a number of centers, the recruitment of men and women was from sites throughout the United States, there was a high rate of adherence to the regimens in each treatment group, a high rate of assessment of the primary end point (low rate of loss

Table 5. *Comparison within and between treatment groups of baseline and end point symptom scores of patients with IC/PBS*

	Mean ± SD MPT				Mean ± SD GTM				
	Baseline (12 pts)	12 Wks (11 pts)	Mean Change (%)	p Value*	Baseline (14 pts)	12 Wks (12 pts)	Mean Change (%)	p Value*	MPT vs GTM p Value†
Pain (0–10)	6.8 ± 2.0	4.2 ± 2.9	−2.5 (−36.8)	0.005	6.7 ± 1.6	5.9 ± 2.0	−0.9 (−13.4)	0.09	0.07
Urinary urgency (0–10)	6.8 ± 1.4	4.0 ± 2.7	−2.7 (−39.7)	0.01	6.7 ± 2.0	6.3 ± 2.5	−0.8 (−11.9)	0.26	0.14
Urinary frequency (0–10)	7.2 ± 1.4	3.5 ± 2.5	−3.6 (−50.0)	0.003	7.6 ± 1.7	6.8 ± 1.8	−1.2 (−15.8)	0.09	0.06
ICSI	13.0 ± 4.8	8.1 ± 4.9	−4.6 (−35.4)	0.02	12.8 ± 4.0	12.9 ± 4.7	0 (0)	0.94	0.01
ICPI	12.1 ± 3.3	7.3 ± 4.7	−4.7 (−38.8)	0.006	11.5 ± 3.0	10.8 ± 4.0	−1.3 (−11.3)	0.09	0.04
FSFI total‡	21.3 ± 7.1	25.3 ± 6.8	5.0 (23.5)	0.002	18.4 ± 10.6	21.7 ± 8.8	1.4 (7.6)	0.75	0.54
SF-12 physical‡	40.8 ± 11.3	42.9 ± 13.2	1.3 (3.2)	0.51	39.6 ± 10.0	38.2 ± 11.6	−4.4 (−11.1)	0.33	0.23
SF-12 mental‡	33.5 ± 12.8	40.6 ± 9.1	6.2 (18.5)	0.11	38.2 ± 12.1	39.2 ± 11.8	1.8 (4.7)	0.50	0.44

* Paired t test, comparison of scores between baseline and week 12.

† Wilcoxon rank sum test, comparison of change scores from baseline to week 12 for MPT and GTM groups.

‡ Sample sizes shown are slightly smaller for some secondary outcomes due to missing values. FSFI total baseline sample sizes are 10 and 12 for MPT and GTM, respectively, and 12-week sample size is 9 for MPT and GTM. Baseline sample size for SF-12 physical and SF-12 mental is 13.

to followup) and a broad range of domains was assessed as outcomes.

There were also several potential limitations of our study. It was not possible to blind study participants to treatment assignment as more than 90% were aware of their treatment group when queried at the end of the study. To compensate for this shortcoming we attempted to keep study coordinators unaware of participant treatment assignment. To make the GTM arm more similar to the MPT arm and to minimize unblinding among participants we originally considered including weekly internal pelvic assessments in patients undergoing GTM. We ultimately decided that internal manipulation, which had no therapeutic intent, could not be justified. In addition, GTM was administered by physical therapists who may have consciously or unconsciously biased the outcome of therapy. To avoid such bias we considered having massage therapists administer GTM while physical therapists administered MPT. We abandoned this idea since the confounding of therapist with treatment would be an added disadvantage.

Importantly this randomized controlled trial was not designed to assess whether myofascial physical therapy is superior to massage therapy for treatment of UCPPS. Such a study would have to allow for optimization of MPT according to the physical abnormalities that are present, and according to response to treatments and performance of massage therapy treatments by licensed massage therapists. Although physical therapists receive some training in massage therapy and are all licensed to practice massage, this is not a therapeutic modality routinely used by most physical therapists. We elected to have our physical therapists perform MPT and GTM treatments to avoid the confounding of therapist and treatment that would have been present if we had decided to have physical therapists perform the MPT and massage therapists perform GTM. Importantly the GTM treatment used in this trial does not represent the standard of care for massage treatment and the results of this study should not be taken to mean that MPT is superior to massage therapy as would be practiced by an expert for UCPPS.

Table 6. *Comparison within and between treatment groups of baseline and end point symptom scores of patients with CP/CPPS*

	Mean ± SD MPT				Mean ± SD GTM				
	Baseline (11 pts)	12 Wks (11 pts)	Mean Change (%)	p Value*	Baseline (10 pts)	12 Wks (9 pts)	Mean Change (%)	p Value*	MPT vs GTM p Value†
NIH-CPSI Total (0–43)	33.5 ± 4.3	19.2 ± 11.1	−14.4 (−43.0)	0.0003	25.8 ± 5.7	18.2 ± 9.6	−6.8 (−26.4)	0.03	0.07
Pain (0–21)	14.2 ± 2.5	8.0 ± 5.7	−6.2 (−43.7)	0.0007	12.7 ± 2.8	8.2 ± 5.6	−4.4 (−34.6)	0.03	0.39
Urinary (0–10)	8.9 ± 1.4	5.0 ± 2.8	−3.9 (−43.8)	0.0002	4.6 ± 2.7	3.9 ± 2.4	−0.3 (−6.5)	0.65	0.007
Quality of life (0–12)	10.4 ± 2.0	6.2 ± 3.8	−4.2 (−40.4)	0.002	8.5 ± 2.0	6.1 ± 3.2	−2.1 (−24.7)	0.05	0.10
ICSI‡	11.3 ± 4.3	6.7 ± 4.8	−5.3 (−46.9)	0.004	5.6 ± 3.0	4.3 ± 2.7	−2.3 (−41.1)	0.02	0.09
ICPI‡	10.4 ± 4.2	5.4 ± 5.0	−5.9 (−56.7)	0.008	3.8 ± 2.9	3.5 ± 3.0	−1.3 (−34.2)	0.48	0.11
Sexual Health Inventory for Men	18.8 ± 7.0	16.4 ± 9.7	−2.5 (−13.3)	0.26	17.1 ± 5.7	18.6 ± 6.6	2.2 (12.9)	0.37	0.28
SF-12 physical‡	40.4 ± 8.2	48.9 ± 10.0	6.1 (15.1)	0.03	46.0 ± 9.0	50.2 ± 8.3	4.2 (9.1)	0.08	0.73
SF-12 mental‡	38.8 ± 10.7	43.7 ± 12.5	5.6 (14.4)	0.10	37.2 ± 10.0	42.9 ± 9.8	5.8 (15.6)	0.06	1.00

* Paired t test, comparison of scores between baseline and week 12.

† Wilcoxon rank sum test, comparison of change scores from baseline to week 12 for MPT and GTM groups.

‡ Sample sizes shown are slightly smaller for some secondary outcomes due to missing values. ICSI and ICPI baseline sample size is 9 for GTM, and 12-week sample sizes are 7 for MPT and 6 for GTM. SF-12 physical and SF-12 mental baseline sample sizes are 10 for MPT and 9 for GTM, and the 12-week sample size is 10 for MPT.

Table 7. *Level of tenderness/pain to palpation across left and right side within muscle groups on pelvic floor examination*

	Av IC/PBS			Av CP/CPPS		
	Baseline	End Point	p Value*	Baseline	End Point	p Value*
MPT (12 IC/PBS, 11 CP/CPPS):						
Anterior levator	3.67	2.00	0.02	3.72	1.64	0.003
Posterior levator	3.83	2.00	0.01	2.45	1.27	0.090
Obturator internus	3.17	1.73	0.01	2.36	0.55	<0.001
Urogenital diaphragm	1.64	1.30	0.13	1.70	0.55	0.13
GTM (14 IC/PBS, 10 CP/CPPS):						
Anterior levator	3.21	2.75	0.64	3.1	2.0	0.02
Posterior levator	3.29	2.42	0.12	2.9	0.78	0.001
Obturator internus	3.07	2.33	0.10	2.6	1.11	0.13
Urogenital diaphragm	2.07	1.42	0.33	1.4	0.22	0.08

* Paired t test.

We also considered alternative comparison treatments including treatment with oral medication or with procedures such as sacral neuromodulation or acupuncture. We abandoned those study designs because alternative treatments that do not involve bodywork cannot provide us with an estimate of the treatment effect that is present simply through meeting weekly with a caring therapist who administers therapeutic touch.

CONCLUSIONS

Our initial encouraging results suggest that a full-scale clinical trial of myofascial physical therapy methods is possible and that MPT may offer meaningful clinical benefit to patients with UCPPS. To determine if our findings can be replicated we are now conducting a second small study comparing MPT and GTM (with a sample size of approximately 90) at 11 sites.

APPENDIX 1

Urological Pelvic Pain Collaborative Research Network Study Group

Northwestern University/Rehab. Institute of Chicago
Colleen Fitzgerald, MD (Co-Investigator)
Suzanne Badillo, PT
Cynthia E. Neville, PT
Darlene Marko, RN
Cleveland Clinic
Jeannette Potts, MD (PI)
Elizabeth O'Dougherty, PT
Donel Murphy, RN
William Beaumont Hospital
Kenneth Peters, MD (PI)
Lisa K. Odabachian, MPT, RN, BSN
Andrea Sanfield, PT
Eleanor Anton, RN
Loyola University
Mary Pat Fitzgerald, MD (PI)
Rhonda K. Kotarinos, MS, PT
Carole Fortman, PT
Rick Halle-Podell, LMT
Judith Senka, RN
Janet Rindels, RN
Lucia Raducanu, RN
Stanford University
Rodney U. Anderson, MD (PI)
Annemarie Cosby, PT
Angie Morey, MS
Christopher K. Payne, MD (PI)
Laura C. Fraser, MPT
Debra Clay, RN
Anna Ramakrishnan, MS
University of Michigan Medical Center
J. Quentin Clemens, MD (PI)
University of Pennsylvania School of Medicine
J. Richard Landis, PhD (PI)
Keith Mickelberg, RN, BSN
Marie Durborow
Ted Barrell, BS
Shannon Chuai, MS
Liyi Cen, MS
The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
John W. Kusek, PhD (Project Officer)
Leroy M. Nyberg, PhD, MD
Christopher Mullins, PhD

APPENDIX 2

Inclusion, Exclusion and Deferral Criteria

Inclusion Criteria:

Participant has signed and dated the appropriate Informed Consent document.

Participant is 18 years old or older.

If female: using an approved method of birth control, or surgically sterile, or of nonchild bearing age with no menstrual period for the past year.

Participant has a clinical diagnosis of IC/PBS or CP/CPPS in the opinion of the investigator.

Participant with IC/PBS has reported a bladder pain/discomfort score of 3 or greater on a 0–10 Likert scale over the previous 4 weeks. This bladder pain/discomfort criterion must be met at each of the 2 baseline screening visits as reported by the participant.

Participant with IC/PBS has reported a symptom score of abnormal urinary frequency of 3 or greater on a 0–10 Likert scale over the previous 4 weeks. This frequency criterion must be met at each of the 2 baseline screening visits as reported by the participant.

Male participant with CP/CPPS has reported a total NIH/CPSI score of 15 or greater. This total score must be met at each of the 2 baseline screening visits. Male participant with CP/CPPS has a nonzero pain domain score on the NIH/CPSI at the time of enrollment.

Participant has had symptoms of discomfort or pain in the pelvic region for at least a 3-month period within the last 6 months.

Current symptoms have been present for less than 3 years.

Presence of tenderness/pain to palpation found by the physician in 1 of the pelvic floor musculature domains during the first baseline screening visit physical examination which is confirmed by the physical therapist at screening visit 2. Presence of tenderness/pain is defined as a mild, moderate or severe finding by the physician at visit 1 and the physical therapist at visit 2. The pelvic floor musculature domains are defined as anterior or posterior levator muscles, obturator internus muscles and urogenital diaphragm (bulbospongiosus, superficial transverse perinei, ischiocavernosus, central tendon/perineal body). The assessments of tenderness/pain at visits 1 and 2 do not need to be identical in severity or location in order for the participant to be eligible.

Exclusion Criteria:

1. Participant has relevant, painful scars on lower abdominal wall that, in the opinion of the study physician or physical therapist, are unlikely to respond to physical therapy without adjuvant therapy such as injection/needling.
2. A positive urine culture (defined as greater than 100,000 cfu/ml). A negative urine culture within 1 month of study enrollment is acceptable.
3. Participant is unable to tolerate insertion of 1 or 2 vaginal examining fingers (eg, vulvar allodynia) or 1 rectal examining finger.
4. Participant had prior course of physical therapy that included manual therapy with connective tissue manipulation by physical therapist for same symptoms. Prior treatment by therapist with biofeedback, electrical stimulation or pelvic floor exercises is not exclusionary.
5. Participant has relevant neurologic disorder that affects bladder and/or neuromuscular function in the opinion of the investigator.
6. Participant has active urethral or ureteral calculi, urethral diverticulum, history of pelvic radiation therapy, tuberculous cystitis, bladder cancer, carcinoma in situ, prostate cancer or urethral cancer.
7. Participant has/reports any severe, debilitating or urgent concurrent medical condition.
8. Participant has a potentially significant pelvic pathology or abnormalities on examination or prior imaging, including prolapse beyond the hymenal ring, pelvic mass, etc that could cause or contribute to the clinical symptoms, or require treatment.

Exclusion criteria for males only:

1. Participant is currently being treated for chronic bacterial prostatitis as documented by a positive urine culture or prior history of recurrent bacterial urinary infections.
2. Participant has unevaluated suspicious prostate examination requiring further evaluation.
3. Participant has unilateral orchialgia without other pelvic symptoms.
4. Participant has an active urethral stricture.

Exclusion criteria for females only:

1. Pregnancy or refusal of medically approved/reliable birth control in women of child bearing potential.
2. Participant has pain, frequency, urgency symptoms present only during menses.

Deferral criteria:

For men: within the last 24 weeks underwent transurethral prostate resection, transurethral prostate incision, transurethral bladder neck incision, transurethral thermotherapy, transurethral needle ablation, balloon dilation of the prostate, open prostatectomy, or any other prostate treatment such as cryotherapy or thermal therapy.

For women: within the past 24 weeks has had vaginal delivery or cesarean section, transvaginal surgery, hysterectomy or prolapse surgery.

APPENDIX 3

Primary Symptom Outcome Assessment Tool

The global response assessment consists of the following question:

"As compared to when you started the study, how would you rate your overall symptoms now?"

1. markedly worse
2. moderately worse
3. slightly worse
4. the same
5. slightly improved
6. moderately improved
7. markedly improved

Participants who indicated they were 6 "moderately" or 7 "markedly" improved are considered intervention responders.

REFERENCES

1. Abrams P, Cardozo L, Fall M et al: The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. Neurourol Urodyn 2002; **21:** 167.
2. Interstitial Cystitis. Edited by Hanno. PM London: Springer-Verlag 1990.
3. Held PJ, Hanno PM, Wein AJ et al: Epidemiology of interstitial cystitis. In: Interstitial Cystitis. Edited by Hanno. PM London: Springer-Verlag 1990; pp 29–48.
4. Temml C, Wehrberger C, Riedl C et al: Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. Eur Urol 2003; **51:** 803.
5. Nickel JC, Teichman JM, Gregoire M et al: Prevalence, diagnosis, characterization and treatment of prostatitis, interstitial cystitis, and epididymitis in outpatient urological practice: the Canadian PIE study. Urology 2005; **66:** 935.
6. Clemens JQ, Link CL, Eggers PW et al: Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urol 2007; **177:** 1390.
7. Leppilahti M, Tammela TLJ, Huhtala H et al: Prevalence of symptoms related to interstitial cystitis in women: a population based study in Finland. J Urol 2002; **168:** 139.
8. Clemens JQ, Meenan RT, O'Keeffe MC et al: Prevalence and incidence of interstitial cystitis in a managed care population. J Urol 2005; **173:** 98.
9. Ibrahim IA, Diokno AC, Killinger KA et al: Prevalence of self-reported interstitial cystitis (IC) and interstitial-cystitis-like symptoms among adult women in the community. Int Urol Nephrol 2007; **39:** 489.
10. Payne CK, Joyce GF, Wise M et al: Interstitial cystitis and painful bladder syndrome. J Urol 2007; **177:** 2042.
11. Collins MM, Stafford RS, O'Leary MP et al: How common is prostatitis? A national survey of physician visits. J Urol 1998; **159:** 1224.
12. Nickel JC, Downey J, Hunter D et al: Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. J Urol 2001; **165:** 842.
13. Peters KM, Carrico DJ, Kalinowski SE et al: Prevalence of pelvic floor dysfunction in patients with interstitial cystitis. Urology 2007; **70:** 16.
14. Shoskes DA, Berger R, Elmi A et al: Muscle tenderness in men with chronic prostatitis/chronic pelvic pain syndrome: the chronic prostatitis cohort study. J Urol 2008; **179:** 556.
15. Lilius HG, Oravisto KJ and Valtonen EJ: Origin of pain in interstitial cystitis. Effect of ultrasound treatment on the concomitant levator ani spasm syndrome. Scand J Urol Nephrol 1973; **7:** 150.
16. Weiss JM: Pelvic floor myofascial trigger points: manual therapy for interstitial cystitis and the urgency-frequency syndrome. J Urol 2001; **166:** 2226.
17. Oyama IA, Rejba A, Lukban JC et al: Modified Thiele massage as therapeutic intervention for female patients with interstitial cystitis and hightone pelvic floor dysfunction. Urology 2004; **64:** 862.
18. Clemens JQ, Nadler RB, Schaeffer AJ et al: Biofeedback, pelvic floor re-education, and bladder training for male chronic pelvic pain syndrome. Urology 2000; **56:** 951.
19. Cornel EB, van Haarst EP, Schaarsberg RW et al: The effect of biofeedback physical therapy in men with Chronic Pelvic Pain Syndrome Type III. Eur Urol 2005; **47:** 607.
20. Anderson RU, Wise D, Sawyer T et al: Integration of myofascial trigger point release and paradoxical relaxation training treatment of chronic pelvic pain in men. J Urol 2005; **174:** 155.
21. Travell and Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual, 2nd ed. Edited by DG Simons, JG Travell and LS Simons. Philadelphia: Lippincott Williams & Wilkins 1998.
22. Benjamin PJ and Tappan FM: Tappan's Handbook of Healing Massage Techniques: Classic, Holistic, and Emerging Methods, 4th ed. Upper Saddle River, New Jersey: Prentice Hall 2005.
23. O'Leary MP, Sant GR, Fowler FJ Jr et al: The interstitial cystitis symptom index and problem index. Urology 1997; **49:** 58.
24. Litwin MS, McNaughton-Collins M, Fowler FJ Jr et al: The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol 1999; **162:** 369.
25. Ware J Jr, Kosinski M and Keller SD: A 12-item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; **34:** 220.
26. Rosen R, Brown C, Heiman J et al: The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000; **26:** 191.
27. Schover LR, Fouladi RT, Warneke CL et al: Defining sexual outcomes after treatment for localized prostate carcinoma. Cancer 2002; **95:** 1773.
28. Cox DR and Oakes D: Analysis of Survival Data. Boca Raton, Florida: Chapman and Hall/CRC Press LLC 1984.