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A longitudinal analysis of urological chronic pelvic pain syndrome flares in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network

Siobhan Sutcliffe*, Robert Gallop†, Hing Hung Henry Lai‡§, Gerald L. Andriole‡, Catherine S. Bradley¶**††, Gisela Chelimsky‡‡, Thomas Chelimsky§§, James Quentin Clemens¶¶, Graham A. Colditz*, Bradley Erickson††, James W. Griffith***, Jayoung Kim†††, John N. Krieger‡‡‡, Jennifer Labus§§§, Bruce D. Naliboff§§§, Larissa V. Rodriguez¶¶¶, Suzette E. Sutherland‡‡‡, Bayley J. Taple*** and John Richard Landis†

*Division of Public Health Sciences, Department of Surgery and the Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO , †Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA , ‡Division of Urologic Surgery, Department of Surgery , §Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO , ¶Department of Obstetrics and Gynecology, Carver College of Medicine University of Iowa , **Department of Epidemiology, College of Public Health , ††Department of Urology, Carver College of Medicine,University of Iowa, Iowa City, IA , ‡‡Department of Pediatrics, Division of Pediatric Gastroenterology , §§Department of Neurology, Medical College of Wisconsin, Milwaukee, WI , ¶¶Division of Neurourology and Pelvic Reconstructive Surgery, Department of Urology, University of Michigan, Ann Arbor, MI , ***Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL , †††Departments of Surgery and Biomedical Sciences, Cedars-Sinai Medical Center,Los Angeles, CA , ‡‡‡Department of Urology, University of Washington, Seattle, WA , §§§Oppenheimer Center for Neurobiology of Stress and Resilience and Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine, University of California – Los Angeles, Los Angeles , and ¶¶¶Institute of Urology, University of Southern California, Beverly Hills, CA, USA

Objective

To describe the frequency, intensity and duration of urological chronic pelvic pain syndrome symptom exacerbations ('flares'), as well as risk factors for these features, in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Epidemiology and Phenotyping longitudinal study.

Participants and Methods

Current flare status ('urological or pelvic pain symptoms that are much worse than usual') was ascertained at each bi-weekly assessment. Flare characteristics, including start date, and current intensity of pelvic pain, urgency and frequency (scales of 0–10), were assessed for participants' first three flares and at three randomly selected times when they did not report a flare. Generalized linear and mixed effects models were used to investigate flare risk factors.

Results

Of the 385 eligible participants, 24.2% reported no flares, 22.9% reported one flare, 28.3% reported 2–3 flares, and 24.6% reported ≥4 flares, up to a maximum of 18 during the 11-month follow-up (median incidence rate = 0.13/bi-weekly assessment, range = 0.00–1.00). Pelvic pain (mean = 2.63-point increase) and urological symptoms (mean = 1.72) were both significantly worse during most flares (60.6%), with considerable within-participant variability (26.2–37.8%). Flare duration varied from 1 to 150 days (94.3% within-participant variability). In adjusted analyses, flares were more common, symptomatic, and/or longer-lasting in women and in those with worse non-flare symptoms, bladder hypersensitivity, and chronic overlapping pain conditions.

Conclusion

In this foundational flare study, we found that pelvic pain and urological symptom flares were common, but variable in frequency and manifestation. We also identified subgroups of participants with more frequent, symptomatic, and/or longer-lasting flares for targeted flare management/prevention and further study.

Keywords

epidemiology, interstitial cystitis, prostatitis, symptom flare-up

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Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) are characterized by persistent pelvic or bladder pain and urological symptoms, such as urgency and frequency. The aetiology of these conditions, collectively referred to as urological chronic pelvic pain syndrome (UCPPS), is unknown and both are difficult to diagnose and treat [1,2]. The conditions occur in ~1–7% of the population [3–6], and contribute to significant reductions in physical and mental health, sexual health and work productivity, as well as considerable personal and societal healthcare expenditures [4,7–11].

Similarly to many other chronic pain conditions, UCPPS symptoms are not static, but instead fluctuate over time. Symptom exacerbations ('flares') vary widely in presentation, with pelvic pain intensity ranging from mild to severe, flare duration from minutes to months, and flare frequency from less than once per year to multiple times per day, based on patient surveys and focus groups [12,13]. A similarly wide range of flare frequency has been observed in the few longitudinal studies conducted to date. In a previous IC/BPS cohort study, 67.9% of participants reported no flares over the 2-year follow-up, whereas 5.7% reported up to 3–4 flares (defined as UTI symptoms) [14]. Similarly, in our small, previous UCPPS longitudinal study, 51.8% of participants reported no flares over the 1-year follow-up, whereas 12.5% reported 3–4 flares (defined as urological or pelvic pain symptoms that are much worse than usual, lasting at least 1 day) over the 20 days they completed symptom diaries [15]. Both of these studies were limited, however, to specific manifestations of flares (UTI symptoms or day/days-long duration), and neither examined risk factors for greater flare burden; therefore, we used data from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Epidemiology and Phenotyping Study to describe the frequency and characteristics of the full range of flares, and risk factors for these features over the 1-year follow-up.

Participants and Methods

Study Design

The MAPP Epidemiology and Phenotyping Study was a 1-year, multi-site longitudinal study designed to study the 'usual-care' natural history of UCPPS and to identify subgroups of patients with possible differing aetiology and clinical course [16,17]. Participants completed an extensive battery of questionnaires at bi-annual in-person visits and a shorter set at online bi-weekly assessments. The MAPP Epidemiology and Phenotyping Study was approved by the institutional review boards at each site and the data coordinating centre. All participants provided written informed consent.

Flare Assessment

Flares were assessed and characterized as part of a case-crossover study of flare triggers embedded into the main longitudinal study [18]. Briefly, at each bi-annual in-person and bi-weekly assessment, participants were asked to report their current flare status by answering the following question: 'Are you currently experiencing a flare of your urological or pelvic pain symptoms? By this we mean, are you currently experiencing symptoms that are much worse than usual' (Table S1). If participants responded affirmatively, they were directed to a second questionnaire, the Brief Flare Risk Factor Questionnaire [17], which included additional questions about their: (i) flare start date to identify individual flares and calculate a crude (truncated) estimate of flare duration; and (ii) current levels of pelvic pain, urgency, and frequency to characterize the intensity of participants' pelvic pain and urological symptoms during flares (using the maximum of urgency and frequency to describe urological symptoms because of their high degree of correlation). This additional questionnaire was administered for the first three reported flares and at three randomly selected times when participants did not report a flare (once per 4-month period). Recalled symptom data, averaged over the past week (which could possibly include some flare and non-flare days), were also used to describe symptoms during flares.

Risk Factor Assessment

Possible risk factors included study quarter; sex; age; duration of symptoms and symptoms of IC/BPS or CP/CPPS at baseline (men only); average non-flare pelvic pain and urological symptom intensity from visit 3 onwards; and baseline self-reported bladder hypersensitivity [19], whole body pain widespreadness [20] and presence and number of chronic overlapping pain conditions (COPCs) [21]. We also examined pelvic pain and urological symptom trajectories [22] from visit 3 onwards as possible correlates of flare burden.

Statistical Analysis

For the flare frequency analyses, we limited the sample to participants who reported their current flare status at least three times. Crude incidence rates were calculated by dividing the number of assessments at which participants reported a flare (not taking into consideration flare start date, as this was assessed for three flares only) by the number of completed assessments per participant. Relative rates were calculated with generalized linear models, using the number of completed assessments as the offset, generalized estimating equations for robust variance estimation, and Poisson,

negative binomial or generalized Poisson distributions, depending on the dispersion of the data [23–25]. Models were initially adjusted for study site, sex, age, and average non-flare pelvic pain and urological symptom intensity as markers of participants' overall clinical status. Adjustment for baseline flare status, which might influence participants' baseline phenotypic characteristics and correlate with greater flare frequency, was also considered, but not retained, because of its minimal influence on risk factor estimates once non-flare symptom intensity was included in the models. Final models were additionally adjusted for variables that remained significantly associated with flare frequency: bladder hypersensitivity and number of COPCs.

For the flare characteristic analyses, we limited the sample to participants who completed the Brief Flare Risk Factor Questionnaire at least twice, once each when they were and were not experiencing a flare. Flares were required to have started in the preceding 2 weeks to avoid double-counting. Changes in symptom intensity during flares and risk factors for more painful flares, those with worse urological symptoms, and longer flares were estimated using linear and generalized linear mixed effects models, clustering flares by participant [26,27]. Cut-off points for more symptomatic flares were determined by classification and regression tree analyses [28] using data from our previous site-specific survey [13]. This survey asked participants to report their average pelvic pain, urgency, frequency (scales of 0–10), and bother (none, only a little, some, and a lot) for flares lasting minutes, hours and days. We used these data to perform two analyses each for pelvic pain and urological symptoms, one to identify cut-off points for flare symptom intensity associated with 'a lot' of bother (≥7 out of 10 for pelvic pain and urological symptoms), and a second to identify cut-off points for change in intensity during flares associated with 'a lot' of bother among participants with non-flare symptom values <7 (≥4 for pain and urological symptoms). These two cut-off points were then combined into one outcome, similarly to previous depression analyses [29]. We used the median flare duration (≥5 days) in the full MAPP study to define longer flares rather than site-specific data because the distribution assessed on the site-specific survey was considerably shorter than in the full study. Within-participant variability in flare intensity and duration was calculated as 1 minus the intra-class correlation coefficient.

Two-sided P values <0.05 were considered statistically significant. All analyses were performed using SAS version 9.4.

Results

Of the 424 enrolled participants, we excluded two who became pregnant and 19 who did not provide flare status information at least three times during follow-up, leaving 403 participants in the analysis. Forty-five percent of participants were men and most identified as white (88.3%; Table S2). The average age was 43.6 years and the average condition duration was 8.60 years. At baseline, participants reported a moderate level of UCPPS symptoms (mean = 5.08–5.56 out of 10) and many had bladder hypersensitivity (82.9%), extrapelvic pain (73.7%) and/or a COPC (38.0%).

Flare Frequency

Participants provided information on their flare status a mean (range) of 17.6 (3–25 [2.0–11.8%]) times, with wide variation in the number of flares reported (range 0–20 [19.5–0.3%] respectively; median incidence rate 0.13/assessment). Consistent with our previous observation of early symptom regression in this cohort, flare frequency was considerably higher at baseline (0.28/assessment) than later during follow-up (0.11/assessment post-visit 12). As this higher baseline flare frequency may not have been representative of participants' typical frequency, but possibly part of their motivation to join MAPP, we limited all further analyses to visit 3 onwards (n = 385 participants). In this more restricted sample, we observed similarly wide variability in flare frequency, with 24.2% of participants reporting no flares, 22.9% 1 flare, 28.3% 2–3 flares, and 24.6% ≥4 flares, up to a maximum of 18 flares over the 11-month follow-up (0.3% of participants; median incidence rate = 0.13/assessment, range = 0.00–1.00/assessment; Fig. S1).

Risk Factors for Greater Flare Frequency

In unadjusted analyses, female sex; younger age; IC/BPS (vs CP/CPPS) symptoms (men only); greater average non-flare pelvic pain and urological symptom intensity; bladder hypersensitivity; extrapelvic pain; several individual COPCs, increasing number of COPCs, and any COPC; and worsening pelvic pain and urological symptom trajectories were each associated with greater flare frequency (Table 1). After adjustment, findings for IC/BPS symptoms (men only), bladder hypersensitivity, ≥2 COPCs, and worsening pain and urological symptom trajectories remained statistically significant.

Flare Characteristics

Among participants who completed the Brief Flare Risk Factor Questionnaire at least twice (n = 807 non-flare and 716 flare assessments from 297 participants), non-flare values ranged from 0 to 10 for both pelvic pain (mean = 3.15) and urological symptoms (mean = 3.35), with four participants reporting values of 10 for pelvic pain and/or urological symptoms (Table 2, Fig. 1). These values were significantly worse during flares (mean = 5.78 for pelvic pain and 5.07 for urological symptoms, ranges: 0–10). Almost all participants reported

Table 1 Relative rates and 95% CIs of flares in participants with urological chronic pelvic pain syndrome (n = 382*) in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Epidemiology and Phenotyping Study, 2009–2013.

	Crude RR (95% CI)	Adjusted RR† (95% CI)	Adjusted RR‡ (95% CI)
Increasing study quarter (continuous)	1.01 (0.92–1.11)	1.05 (0.96–1.15)	1.04 (0.96–1.14)
Female sex	1.48 (1.20–1.82)	1.29 (1.03–1.61)	1.16 (0.92–1.46)
Increasing age (continuous in years)	0.84 (0.75–0.94)	0.88 (0.79–0.99)	0.92 (0.82–1.03)
Increasing symptom duration (continuous in years)	0.97 (0.87–1.08)	0.95 (0.84–1.08)	0.94 (0.83–1.06)
Baseline IC/BPS vs CP/CPPS symptoms (males only)	1.42 (1.01–2.01)	1.71 (1.03–2.85)	1.62 (1.00–2.64)
Average non-flare pelvic pain intensity (continuous from 0 to 10)	1.13 (1.08–1.18)	1.02 (0.95–1.09)	1.03 (0.96–1.11)
Average non-flare urological symptom intensity (continuous from 0 to 10)	1.14 (1.09–1.19)	1.11 (1.04–1.18)	1.06 (0.98–1.14)
Bladder hypersensitivity			
Neither painful filling nor urgency	1.00	1.00	1.00
Either painful filling or urgency	1.63 (1.18–2.26)	1.55 (1.12–2.15)	1.58 (1.15–2.20)
Both painful filling and urgency	2.19 (1.61–2.96)	1.75 (1.29–2.37)	1.73 (1.28–2.35)
Number of extrapelvic regions with pain§			
0	1.00	1.00	1.00
1–2	1.34 (1.03–1.74)	1.21 (0.94–1.56)	1.16 (0.90–1.50)
3–7	1.34 (1.03–1.75)	1.08 (0.83–1.41)	1.00 (0.75–1.33)
COPC			
Chronic fatigue syndrome	2.04 (1.53–2.73)	1.43 (1.08–1.90)	1.16 (0.82–1.63)
Fibromyalgia	1.41 (0.96–2.07)	1.01 (0.74–1.38)	0.71 (0.50–1.03)
Irritable bowel syndrome	1.22 (0.98–1.53)	1.05 (0.85–1.29)	0.96 (0.77–1.19)
Migraines	1.44 (1.13–1.83)	1.26 (0.99–1.60)	1.12 (0.83–1.51)
Temporomandibular joint disorder	1.31 (1.02–1.68)	1.08 (0.86–1.37)	0.82 (0.59–1.14)
Vulvodynia	1.41 (1.02–1.95)	1.22 (0.90–1.66)	1.15 (0.84–1.55)
Number of conditions			
0	1.00	1.00	1.00
1	1.25 (0.98–1.59)	1.14 (0.88–1.48)	1.13 (0.87–1.45)
2 or more	1.82 (1.40–2.36)	1.34 (1.03–1.75)	1.30 (1.01–1.68)
Any condition	1.33 (1.07–1.64)	1.04 (0.85–1.27)	0.89 (0.70–1.14)
Pelvic pain trajectory over follow-up			
Improving	1.00	1.00	1.00
Stable	0.95 (0.73–1.24)	0.83 (0.65–1.06)	0.85 (0.67–1.08)
Worsening	1.47 (1.15–1.87)	1.39 (1.10–1.75)	1.42 (1.13–1.78)
Urological symptom trajectory over follow-up			
Improving	1.00	1.00	1.00
Stable	0.95 (0.73–1.23)	0.88 (0.69–1.12)	0.90 (0.71–1.14)
Worsening	1.41 (1.11–1.79)	1.34 (1.05–1.70)	1.33 (1.05–1.68)

*COPC, chronic overlapping pain condition; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; IC/BPS, interstitial cystitis/bladder pain syndrome; RR, relative rate. *Excludes three participants who reported flares at all bi-weekly assessments. †Adjusted for site, sex, age, and average non-flare symptom intensity, as appropriate. ‡Adjusted for site, sex, age, average non-flare symptom intensity, bladder hypersensitivity, and number of COPCs, as appropriate. §Seven extrapelvic regions (back, head, right leg, left leg, right arm, left arm, and trunk) were created similar to previous analyses, using data from the Body Pain Inventory.*

values >0 for pelvic pain and urological symptoms during flares, except for two with all values of 0. On average, symptoms increased by 2.63 (range: −4 to 9) for pelvic pain and 1.72 (range: −6 to 8) for urological symptoms during flares. Similar increases were observed for other UCPPS symptoms and overall pain in the week before participants' flare assessments. With respect to flare duration (reported for 579 flares), 20.0% of flares had lasted 1–2 days by the time of participants' flare assessment, 40.2% 3–6 days, 24.2% 7–10 days, and 15.5% >10 days (range = 1–150 days). In general, current pelvic pain decreased slightly, but significantly, with increasing flare duration, whereas current urological symptoms increased slightly with increasing duration.

Considering patterns of symptoms, most flares involved an increase (≥1 point above non-flare symptoms) in both pelvic pain and urological symptoms (60.6%), with smaller percentages involving increases in pelvic pain (20.1%) or urological symptoms only (5.8%). Four percent (4.3%) of flares had stable symptoms and 9.2% had a decrease (Fig. 1). When flares from the same participant were examined, a high degree of within-participant variability was observed (pelvic pain = 37.8% of the total variance, urological symptoms = 26.2%, and duration = 94.3%), indicating that participants did not always experience the same intensity or duration of symptoms during flares, but that these characteristics could vary.

Risk Factors for Flare Characteristics

In unadjusted analyses, female sex, worse non-flare pelvic pain and urological symptom intensity, and fibromyalgia were associated with more painful flares (Table 3). With the exception of fibromyalgia, these factors were also associated with flares with worse urological symptoms, as was earlier study quarter, longer condition duration, IC/BPS symptoms (men only), and bladder hypersensitivity. Having a stable urological symptom trajectory was protective for flares with worse urological symptoms. Finally, worse non-flare pain

Table 2 Flare and non-flare symptoms in participants with urological chronic pelvic pain syndrome in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Epidemiology and Phenotyping Study, 2009–2013.

	N	Non-flare (mean [SD]/%) *	Flare (mean [SD]/%)†	Mean change during flares	*P*
UCPPS symptoms					
Current symptoms					
Pelvic pain (range: 0–10)	287	3.15 (2.31)	5.78 (2.15) ‡	2.63	<0.0001
Urological symptoms (maximum of urgency and frequency, range: 0–10)	289	3.35 (2.47)	5.07 (2.69) §	1.72	<0.0001
Symptoms in the past week					
Any pain or discomfort in the (%)					
Women					
Entrance to the vagina	173	38.5	52.9	14.4	0.0014
Vagina	174	39.2	52.2	13.0	0.004
Urethra	175	44.9	63.6	18.7	<0.0001
Men					
Tip of the penis (not related to urination)	120	32.7	45.8	13.1	0.02
Testicles	120	29.2	38.2	9.0	0.11
Perineum	120	43.5	49.8	6.3	0.28
Any genital site	295	63.0	79.2	16.2	<0.0001
Number of genital sites with pain (range: 0–3)	295	1.15 (1.09)	1.53 (1.08)	0.38	<0.0001
Any pain or burning during urination	295	41.6	58.7	17.1	<0.0001
Any pain or discomfort during or after sexual intercourse	272	32.2	43.3	11.1	0.002
Any pain or discomfort with bladder filling	295	48.5	61.4	12.9	0.0006
Any pain or discomfort relieved by voiding	295	54.2	63.7	9.4	0.011
Frequency of a sensation of incomplete emptying (0 = not at all to 5 = almost always)	295	1.81 (1.65)	2.16 (1.69)	0.35	0.007
Overall symptoms					
Current symptoms					
Overall whole body pain (range: 0–10)¶	122	3.41 (2.56)	4.36 (2.59)	0.95	0.004
Symptoms in the past week					
Worst pain (range: 0–10)¶	122	5.42 (2.88)	6.51 (2.49)	1.10	0.001
Average pain (range: 0–10)¶	120	3.88 (2.27)	4.63 (2.16)	0.74	0.009

*UCPPS, urological chronic pelvic pain syndrome. *Includes a maximum of 807 non-flare values. †Includes a maximum of 716 flare values. ‡Taking flare duration into account (n = 579 flares), these values were 6.09 for 1–3 day-long flares, 5.70 for 4–5 day-long flares, 5.75 for 6–8 day-long flares, and 5.62 for >8 day-long flares (P < 0.0001). §These values were 5.10 for 1–3 day-long flares, 5.10 for 4–5 day-long flares, 5.00 for 6–8 day-long flares, and 5.14 for >8 day-long flares (P < 0.0001). ¶Assessed by the Brief Pain Inventory, which was administered every 2 months. Responses collected within 2 weeks of a flare/non-flare assessment were used.*

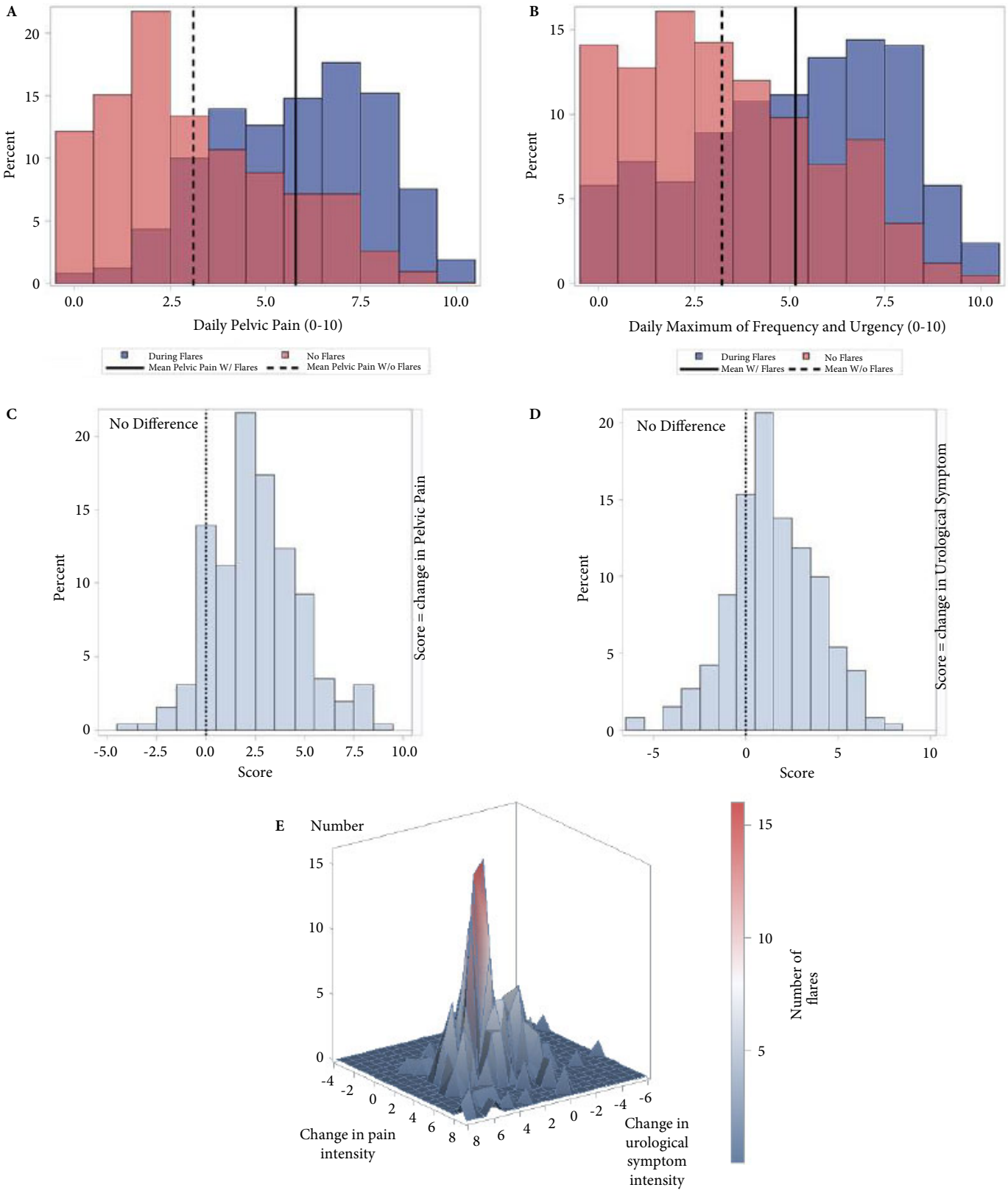
intensity, irritable bowel syndrome, and any COPC were associated with longer flares.

In adjusted analyses, female sex and greater non-flare pelvic pain intensity remained significantly associated with more painful flares, and female sex, greater non-flare urological symptom intensity, and bladder hypersensitivity remained significantly associated with flares with worse urological symptoms. Older age increased the odds of flares with worse urological symptoms. Finally, worse non-flare pain intensity, irritable bowel syndrome, and any COPC remained significantly associated with longer flares. Having a stable pelvic pain trajectory was protective.

Discussion

In this foundational flare study – the largest and most comprehensive to date – we found that pelvic pain and urological symptom flares were common, but variable in frequency, intensity and duration. This variability was observed both across and within participants. We also found that female sex, worse non-flare symptoms, and bladder

Fig. 1 Flare and non-flare symptoms in participants with urological chronic pelvic pain syndrome in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Epidemiology and Phenotyping Study, 2009–2013. On each bi-weekly assessment of the 1-year MAPP study follow-up, participants were asked to report whether they were currently experience a flare of their urological or pelvic pain symptoms (i.e. 'symptoms that are much worse than usual'). If participants responded affirmatively, they were directed to a second questionnaire in which they were asked about their current intensity of pelvic pain, urinary urgency and frequency on scales of 0–10. This questionnaire was completed for the first three reported flares. Participants were also asked to complete the second questionnaire at three randomly selected times when they did not report a flare. (**A**) Describes the distribution of pelvic pain intensity reported at non-flare (light pink) and flare (blue) assessments. Overlapping values are indicated in dark pink. (**B**) Describes the distribution of urological symptom intensity (i.e. the maximum of urgency and frequency intensity) at non-flare (light pink) and flare (blue) assessments. Changes in pelvic pain and urological symptom intensity during flares are described in (**C** and **D**), using the closest non-flare and flare assessments for comparison. (**E**) presents the joint distribution of changes in pelvic pain and urological symptom intensity during flares.


A
Percent
Daily Pelvic Pain (0-10)
During Flares
No Flares
Mean Pelvic Pain W/ Flares
Mean Pelvic Pain W/o Flares
B
Percent
Daily Maximum of Frequency and Urgency (0-10)
During Flares
No Flares
Mean W/ Flares
Mean W/o Flares
C
No Difference
Percent
Score
Score = change in Pelvic Pain
D
No Difference
Percent
Score
Score = change in Urological Symptom
E
Number
Change in pain intensity
Change in urological symptom intensity
Number of flares

hypersensitivity or COPCs were independently associated with greater flare burden, including greater flare frequency, symptom intensity and/or duration.

To our knowledge, only two previous studies have documented flare frequency over time in participants in order to avoid recall inaccuracy [14,15]. Similarly to our analysis, these studies (one of which included a small subset of our participants) observed a wide range in flare frequency, although one was considerably lower (67.9%, 0 flares; 5.7%, 3–4 flares) than our distribution (24.4% 0 flares; 20.5%, 3–4 flares), most likely because of its more restrictive flare definition (i.e. UTI symptoms). It is also possible that we double-counted flares lasting >2 weeks, as these could have been captured on more than one bi-weekly assessment. Nevertheless, our estimates are still probably lower than the true frequency of flares because we did not capture flares that occurred between bi-weekly assessments. Our estimates also did not distinguish flares by intensity or duration, both of which have been found to contribute to their degree of impact and bother [12,13]. Future studies should therefore consider using additional methods, such as diaries or ecological momentary assessment, to obtain more accurate estimates of flare frequency, both overall and by flare type.

Similarly to flare frequency, our descriptive findings for flare characteristics are consistent with those from the small number of studies conducted to date [12,13,15]. These studies, many of which included a small subset of our participants, found that, although most flares involved significant increases in both pelvic pain and urological symptoms, they could also vary in type (pelvic pain only, urological symptoms only, or both) and intensity (mild to severe) of symptoms, both across and within participants. These findings are consistent with our observations of: (i) increases in both pelvic pain and urological symptoms in a large proportion of flares (60.7%); (ii) wide ranges in flare symptom intensity (0–10); (iii) wide ranges in changes in symptom intensity during flares (−6 to 9); and (iv) considerable within-participant variability in symptom intensity (26.2–37.8% of the total variance). Notably, our large sample size also allowed us to observe a small number of flares not previously described by other studies with seemingly stable or decreasing symptom levels. These unexpected flares may potentially be explained by: (i) the inclusion of non-flare symptom values of 10, precluding notable symptom increases during flares; (ii) changes in symptoms during flares besides pelvic pain, urgency and frequency, such as genital pain or pain with urination only; (iii) long time lags between non-flare and flare assessments, making these values less comparable; and (iv) participant error. Similarly to previous studies, we also observed wide variability in flare duration, ranging from 1 to 150 days; however, our distribution was probably shifted more towards longer flares than were previous surveys and focus groups because of length-biased sampling [30] (i.e. longer flares would be more likely to be captured on bi-weekly assessments than shorter flares). Alternatively, our estimates may be slightly under-estimated because flare duration was truncated at bi-weekly assessments. More accurate estimates would require following participants for the full duration of their flare.

Finally, our findings for flare risk factors are consistent with those from the limited literature on this topic to date [13–15]. In their cohort study of patients with IC/BPS, Stanford and McMurphy [14] observed that participants with higher average baseline pain/urgency/frequency scores were borderline significantly more likely to report a UTI-symptom flare than those with lower scores, similar to our observation of crude and lesser-adjusted positive associations for greater non-flare symptom intensity with flare frequency. We also found that participants with worse non-flare symptoms were more likely to report flares with greater symptom intensity and duration (pelvic pain only), and that those with worsening pelvic pain and urological symptom trajectories were more likely to report greater flare frequency, consistent with focus group participant reports that non-flare and flare symptoms worsen and improve together, i.e. that when their condition is 'bad', they experience worse non-flare symptoms, as well as more frequent, symptomatic and longer flares [12]. An additional novel finding from the present study was that associations between non-flare symptoms and flare frequency attenuated after adjustment for bladder hypersensitivity and number of COPCs, suggesting they may have been explained by these two characteristics rather than by a link between worse non-flare symptoms and greater flare frequency; for instance, as a marker of overall worse clinical status.

With respect to sex, we previously observed that women were more likely to report days-long flares [13,15] and less likely to report minutes-long flares than men in minimally adjusted, site-specific analyses [13]. As the present study design may have been more likely to capture day(s)- rather than minutes-long flares, we believe these previous findings are consistent with our crude and lesser-adjusted observations of greater flare frequency among women than men and, at least, not inconsistent with our observation of no difference in flare duration by sex among the sample of longer flares likely captured by our study design.

Further novel findings from the present study were as follows: (i) that associations between female sex and greater flare frequency attenuated after adjustment for bladder hypersensitivity and COPCs, suggesting that they may have been explained by these two factors; and (ii) that women

Table 3 Odds ratios and 95% CIs of greater flare pelvic pain intensity, urological symptom intensity, and duration in participants with urological chronic pelvic pain syndrome (n = 286) in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Epidemiology and Phenotyping Study, 2009–2013.

	Pelvic pain intensity[‡]			Urological symptom intensity[§]			Duration[¶]		
	Crude OR	Adjusted OR[††]	Adjusted OR[‡‡]	Crude OR	Adjusted OR[††]	Adjusted OR[‡‡]	Crude OR	Adjusted OR[††]	Adjusted OR[‡‡]
Increasing study quarter (continuous)	0.88	0.95	0.96	0.79*	0.86	0.87	0.87	0.87	0.87
Female sex	2.16***	2.00**	2.12**	2.29***	2.33**	2.54***	1.09	0.99	1.01
Increasing age (continuous in years)	0.86	0.98	0.96	1.12	1.35*	1.30*	0.97	1.01	1.01
Increasing symptom duration (continuous in years)	1.11	1.04	1.05	1.23*	1.13	1.14	1.07	1.02	1.03
Baseline IC/BPS vs CP/CPPS symptoms (men only)	1.38	1.47	1.51	4.04*	2.58	1.91	0.63	0.70	0.72
Average non-flare pelvic pain intensity (continuous from 0 to 10)	1.39***	1.28**	1.29**	1.30***	0.95	0.96	1.09*	1.17*	1.17*
Average non-flare urological symptom intensity (continuous from 0 to 10)	1.32***	1.10	1.11	1.46***	1.51***	1.50***	1.03	0.93	0.94
Increasing bladder hypersensitivity									
Neither painful filling or urgency	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Either painful filling or urgency	1.08	0.85	0.82	5.44***	5.16**	4.77**	0.87	1.02	1.03
Both painful filling and urgency	1.67†	0.96	0.96	7.08***	4.29**	4.19**	0.77	0.83	0.83
Number of non-pelvic regions with pain[§§]									
0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1–2	0.76	0.56†	0.57†	0.70	0.55†	0.58†	1.58†	1.42	1.42
3–7	1.21	0.75	0.81	1.03	0.57†	0.69	1.63†	1.58	1.59
COPCs									
Chronic fatigue syndrome	1.62†	0.62	0.64	1.64	0.64	0.89	0.84	0.89	0.80
Fibromyalgia	2.34*	1.46	2.49†	1.27	0.70	1.27	1.11	0.97	0.90
Irritable bowel syndrome	1.18	0.90	0.95	1.06	0.72	0.77	1.55*	1.68*	1.77*
Migraines	1.39	1.16	1.61	0.96	0.75	1.13	1.16	1.23	1.32
Temporomandibular joint disorder	0.97	0.65	0.62	0.97	0.64	0.90	0.85	0.88	0.73
Vulvodynia	1.03	0.80	0.85	1.30	0.82	0.95	1.14	1.22	1.22
Number of conditions									
0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1	1.03	0.85	0.85	0.76	0.56†	0.54†	1.18	1.21	1.22
≥2	1.63†	0.78	0.78	1.33	0.54†	0.52†	1.03	1.15	1.16
Any condition	1.37	0.88	0.96	1.04	0.63†	0.69	1.63*	1.74**	2.02**
Pelvic pain trajectory over follow-up									
Improving	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Stable	0.90	0.69	0.70	0.74	0.60†	0.66	0.73	0.56*	0.53*
Worsening	0.71	0.65	0.65	0.70	0.61†	0.67	0.82	0.76	0.73
Urological symptom trajectory over follow-up									
Improving	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Stable	0.86	0.75	0.75	0.57*	0.54*	0.57†	0.81	0.73	0.71
Worsening	1.22	1.07	1.08	1.32	1.14	1.11	0.69	0.65†	0.66†

*COPC, chronic overlapping pain condition; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; IC/BPS, interstitial cystitis/bladder pain syndrome; OR, odds ratio. †0.05 ≤ P<0.10; *0.01 ≤ P<0.05; **0.001 ≤ P<0.01, ***P < 0.001. ‡Defined as a change in pelvic pain of ≥4 or a level of pelvic pain ≥7 on a scale of 0–10 during a flare. §Defined as a change in urological symptoms (maximum of urgency and frequency) of ≥4 or a level of urological symptoms ≥7 on a scale of 0–10 during a flare. ¶Defined as a duration ≥5 days, the median flare duration in this population. ††Adjusted for site, sex, age and average non-flare symptom intensity, as appropriate. ‡‡Adjusted for site, sex, age, average non-flare symptom intensity, bladder hypersensitivity and number of COPCs, as appropriate. §§Seven extrapelvic regions (back, head, right leg, left leg, right arm, left arm and trunk) were created similarly to previous analyses, using data from the Body Pain Inventory.*

were independently more likely to report greater flare symptom intensity than men.

In addition to non-flare symptoms and sex, we found that participants with bladder hypersensitivity or COPCs (various individual, any, or multiple COPCs), but not extrapelvic pain, had greater flare frequency, worse urological symptoms during flares (bladder sensitivity only), and longer flares (COPCs only) in adjusted analyses. These novel, but slightly contradictory findings suggest that both peripheral and central pain mechanisms may potentially contribute to flare burden. Finally, although some associations did not persist in adjusted analyses, this does not mean that certain subgroups did not experience greater flare burden, only that their burden was more related to their bladder hypersensitivity and COPCs than to other characteristics.

Although the present study is the largest and most detailed cohort study of flares to date, it is still limited by its use of data collected for a different research purpose (i.e. to identify flare triggers with purposefully minimal ascertainment/characterization of flares). As such, we did not have information on flares that occurred between bi-weekly assessments, the full duration of flares, or characteristics of all flares (only a maximum of three flares/participant). These limitations reduced our ability to: (i) describe the frequency of flares overall and by symptom intensity and duration; (ii) describe the full distribution of flare intensity and duration; and (iii) detect associations, especially for flare intensity and duration, as the 1–3 flares included per participant may not have been representative of their typical flare experience. Finally, a further major limitation is our minimal collection of information on UCPPS therapies, precluding analysis of their influence on flare burden.

In summary, we found that the majority of participants experienced at least one flare of their pelvic pain and urological symptoms during the 11-month follow-up, with wide variability in flare frequency, intensity, and duration between and within participants. In general, flares were independently more common, symptomatic, and/or longer-lasting in women, and in those with worse non-flare symptoms, bladder hypersensitivity, or COPCs. Together, these findings provide foundational, descriptive information on flares and identify patient subgroups to target and study further for flare management and prevention.

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Conflict of Interest

H. Henry Lai: Clinical trial of an investigational drug for Allergan; Scientific Advisory Board for Aquinox and Teva; Product registry for Medtronic. Gisela Chelimsky: Co-owner of PAinStakers LLC. Jennifer Labus: Grants from University of California – Los Angeles. Suzette E. Sutherland: Unrestricted educational grant/Advisory Board/Consultant for Boston Scientific; Clinical research for Fempulse, Pelvital, and Allergan; Advisory Board/Consultant for Axonics. Other authors declare no conflict of interest.

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Correspondence: Siobhan Sutcliffe, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, 600 S. Taylor Ave., Box 8100, Rm 208S, St. Louis, MO 63110, USA.

e-mail: sutcliffes@wustl.edu

Abbreviations: COPC, chronic overlapping pain condition; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; IC/BPS, interstitial cystitis/bladder pain syndrome; MAPP, Multidisciplinary Approach to the Study of Chronic Pelvic Pain; UCPPS, urological chronic pelvic pain syndrome.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of information used to characterize flares and determine risk factors for and correlates of flare burden.
Table S2. Baseline demographic and clinical characteristics of all urological chronic pelvic pain syndrome participants combined and separately for those in the flare frequency and flare characteristics analyses; Multidisciplinary Approach to the Study of Chronic Pelvic Pain Epidemiology and Phenotyping Study, 2009–2013.
Fig. S1. Frequency of urological chronic pelvic pain syndrome flares in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Epidemiology and Phenotyping Study, 2009–2013. On each bi-weekly assessment of the MAPP study, participants were asked to report whether they were currently experiencing a flare of their urological or pelvic pain symptoms (i.e. 'symptoms that are much worse than usual'). The percentage of participants who reported each number of flares over the last 11 months of the 1-year study is plotted.