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BLADDER

Longitudinal Changes in the Pelvic Pain Only and Widespread Pain Phenotypes Over One Year in the MAPP-I Urologic Chronic Pelvic Pain Syndrome (UCPPS) Cohort

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To examine how often urologic chronic pelvic pain syndrome (UCPPS) patients progressed from Pelvic Pain Only at baseline to Widespread Pain, or vice versa, during one-year longitudinal follow-up. Men and women with UCPPS enrolled in the MAPP-I Epidemiology and Phenotyping Study completed a self-report body map to indicate their locations of pain every 2 months over 12 months. Patients were categorized at each assessment into one of three pain phenotypes: 1) Pelvic Pain Only, 2) an Intermediate group, 3) Widespread Pain. Only patients who completed 3 or more follow-ups were included in this longitudinal analysis. The primary outcome measure was pain classification at the majority (≥60%) of follow-up assessments. Longitudinal trends of somatic symptom burden were also assessed. Among the 93 UCPPS participants with Pelvic Pain Only at baseline, only 2% (n=2) showed a Widespread Pain phenotype for the majority of assessments over 12 months. Among the 121 participants who had Widespread Pain at baseline, 6% (n=7) demonstrated Pelvic Pain Only for the majority of assessments over 12 months. Over half of participants (≥53%) stayed in their baseline phenotypic group. Somatic symptom burden remained stable over 12 months for each of the groups with high intra-class correlation coefficient (0.67 to 0.82). It was uncommon for UCPPS patients to progress from Pelvic Pain Only to Widespread Pain, or vice versa, over 12 months. These data suggest that Pelvic Pain Only and Widespread Pain are distinct UCPPS phenotypes that are relatively stable over 12 months of follow up.

Reliability and Validity of Pain and Urinary Symptom Severity Assessment in Urologic Chronic Pelvic Pain; A MAPP Network Analysis

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To assess reliability and validity of an efficient severity assessment for pelvic pain and urinary symptoms in urologic chronic pelvic pain syndrome (UCPPS), which consists of interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). 578 patients were assessed using brief, empirically derived self-report scales for Pelvic Pain Severity (PPS) and Urinary Symptoms Severity (USS) four times during a one-month period and baseline clinic visit that included urologic, pain and illness-impact measures. Mild, moderate and severe categories on each dimension were examined for measurement stability and construct validity. PPS and USS severity categories had adequate reliability and both discriminant validity (differential relationships with specific clinical and self-report measures) and convergent validity (common association with non-urological somatic symptoms). For example, increasing PPS was associated with pelvic tenderness and widespread pelvic pain, whereas USS was associated with urgency during a bladder filling test and increased sensory sensitivity. PPS and USS categories were independently associated with non-urological pain and emotional distress. A descriptive analysis identified higher likelihood characteristics associated with having moderate to severe PPS or USS or both. Lack of sex interactions indicated that the measures are comparable in IC/BPS and CP/CPPS. Women and men with UCPPS can be reliably subgrouped using brief self-report measures of mild, moderate or severe pelvic pain and urinary symptoms. Comparisons with a broad range of clinical variables demonstrate the validity and potential clinical utility of these classifications, including use in clinical trials, health services and biological research.

Role of hyperpolarization-activated cyclic nucleotide-gated channels in aging bladder phenotype

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To assess the functional role of Hyperpolarization-activated cyclic nucleotide-gated gated channel (HCN) subtypes in the aging bladder phenotype characterized by diminished bladder volume sensation (BVS) with or without the detrusor instability (DI). Expression of HCN subtypes was examined by quantitative RT-PCR and Western blot in aged male Fisher 344 rats (n = 15) and young rats (n = 15). Nocturnal urination and awake cystometry (CMG) were assessed in presence and absence of a steady state HCN channel blockade achieved with daily oral gavage of vehicle or Ivabradine (HCN blocker) 6 mg/kg for 7 days. The association of BVS with the age-related downregulation (~30%) of cAMP sensitive HCN1, HCN2 subtypes, and (~50%) upregulation of cAMP insensitive HCN3 subtype is evinced by the doubling in the mean urine volume of nocturnal voids (0.82 ± 0.22 mL vs 0.41 ± 0.12 mL; n = 10; $p < 0.05$) predicting an age-related rise in the micturition volume threshold ($p < 0.0001$) in CMG, which is raised further by Ivabradine treatment ($p < 0.0005$). Ivabradine also doubled non-voiding contractions (NVC) and maximum voiding pressure (MVP) in young and aged rats, respectively ($p < 0.0001$) to abolish the age-related, innate two -fold elevation in NVC not accompanied with MVP rise in untreated aged rats ($p < 0.005$). The age-related HCN downregulation is mechanistically linked to the exhibition of aging bladder phenotype with the manifestation of DI following steady state blockade of HCN

channels in Ivabradine treated young rats. The amplification of MVP in aged rats mediated by FDA approved Ivabradine hints at potential repurposing opportunity in detrusor underactivity.

The O'Leary-Sant Interstitial Cystitis Symptom Index is a clinically useful indicator of treatment outcome in patients with interstitial cystitis/bladder pain syndrome with Hunner lesions: A post hoc analysis of the Japanese phase III trial of KRP-116D, 50% dimethyl sulfoxide solution

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To evaluate the efficacy of intravesical KRP-116D, 50% dimethyl sulfoxide solution, in interstitial cystitis/bladder pain syndrome patients with Hunner lesions (Hunner-type interstitial cystitis), and to evaluate the correlations between efficacy variables and global response assessment to determine what constitutes a minimal clinically important change. We performed a post hoc analysis of the Japanese phase III trial of KRP-116D. Changes at Week 12 from baseline in objective and subjective outcomes were compared between the KRP-116D and placebo groups in Hunner-type interstitial cystitis or non-Hunner-type interstitial cystitis patients. Correlations between efficacy variables at Week 12 and global response assessment were analyzed. Area under the receiver operating characteristic curve and the cut-off value of efficacy valuables were calculated to determine clinically meaningful changes. The effectiveness of intravesical treatment with KRP-116D was demonstrated in Hunner-type interstitial cystitis, but not in non-Hunner-type interstitial cystitis patients. Global response assessment was closely correlated with subjective outcomes including O'Leary-Sant Interstitial Cystitis Symptom Index, O'Leary-Sant Interstitial Cystitis Problem Index, and a numeric rating scale for bladder pain, but was less correlated with voiding variables including micturition frequency, voided volume, and maximum voided volume. In the receiver operating characteristic curve analyses, the cut-off value for the O'Leary-Sant Interstitial Cystitis Symptom Index was -5 (sensitivity 81.3%, specificity 83.3%). Clinical benefit of intravesical KRP-116D in Hunner-type interstitial cystitis patients was confirmed in this post hoc analysis. A five-point reduction in O'Leary-Sant Interstitial Cystitis Symptom Index is a clinically meaningful indicator for assessing patient satisfaction with KRP-116D treatment in patients with Hunner-type interstitial cystitis.

PROSTATE

A retrospective review of canine benign prostatic hyperplasia with and without prostatitis

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Benign prostatic hyperplasia (BPH) is the most common prostatic disorder in older intact male dogs, but despite its prevalence, there are inconsistencies in clinical diagnosis and treatment. Although prostate size was historically considered the hallmark feature of BPH in men, currently, there is only a weak correlation between prostate size and clinical severity. We performed a retrospective cohort study with the primary objective of assessing clinical signs, ultrasonographic findings, treatments, and outcomes in dogs diagnosed with BPH, with and without concurrent prostatitis. We reviewed medical records and obtained data on presenting signs, prostatic imaging, and prevalence of concurrent bacteriuria. Prostate size was determined by ultrasonography and compared to the calculated expected size based on patient age and weight. Treatment and outcome were described for the cases with a minimum 2 months follow-up. Median age of dogs diagnosed with BPH was 8 years. Clinical signs were present in 16/25 dogs and scored as mild to moderate (median Zambelli's Symptom Index for BPH score 12). The median prostatic volume to body mass ratio was 1.60 mm3/kg. Prostate size did not correlate with the symptom severity. Concurrent bacteriuria was confirmed in 4/25 cases via bacterial culture and/or cytology. Treatments pursued and responses were only available in a subpopulation of dogs (n = 9) and were highly variable. Studies are needed to determine if current treatment options for BPH in dogs resolve associated clinical signs in addition to reducing prostate size.

Benign Prostatic Hyperplasia/Obstruction Ameliorated Using a Soluble Guanylate Cyclase Activator

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Benign prostatic hyperplasia (BPH) is a feature of ageing males. Up to half demonstrate bladder outlet obstruction (BOO) with associated lower urinary tract symptoms (LUTS) including bladder overactivity. Current therapies to reduce obstruction, such as α1-adrenoceptor antagonists and 5α-reductase inhibitors, are not effective in all patients. The phosphodiesterase-5 inhibitor (PDE5I), tadalafil, is also approved to treat BPH and LUTS suggesting a role for nitric oxide (NO•), soluble guanylate cyclase (sGC), and cGMP signalling pathways. However, PDE5I refractoriness can develop for reasons including nitrergic nerve damage and decreased NO• production, or inflammation-related oxidation of the sGC haem group, normally maintained in a reduced state by the cofactor, cytochrome-b5-reductase 3 (CYB5R3). sGC activators, such as cinaciguat (BAY 58-2667), have been developed to enhance sGC activity in the absence of NO• or when sGC is oxidised. Accordingly, their effects on the prostate and LUT function of aged mice were evaluated. Aged mice (≥24 months) demonstrated a functional BPH/BOO phenotype, compared to adult animals (2-12 months), with low, delayed voiding responses and elevated intravesical pressures as measured by telemetric cystometry. This was consistent with outflow tract histological and molecular data that showed urethral constriction, increased prostate weight, greater collagen deposition and cellular hyperplasia. All changes in aged animals were attenuated by daily oral treatment

with cinaciguat for two weeks, without effect on serum testosterone levels. Cinaciguat had only transient (1 h) cardiovascular effects with oral gavage suggesting a positive safety profile. The benefit of cinaciguat was suggested by its reversal of an overactive cystometric profile in CYB5R3 smooth muscle knock-out mice that mirrors a profile of oxidative dysfunction where PDE5I may not be effective. Thus, the aged male mouse is a suitable model for BPH-induced BOO and cinaciguat has a demonstrated ability to reduce prostate-induced obstruction and consequent effects on bladder function.

STONES

Sulfamethoxazole-induced sulfamethoxazole urolithiasis: a case report

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Drug-induced urolithiasis falls into two categories: drug-induced and metabolically-induced. Certain antimicrobials are associated with each; sulfonamides are associated with drug- or metabolite-containing calculi when taken in large doses over a long period of time. Trimethoprim-sulfamethoxazole, a member of the sulfonamide family, is a rare cause of drug-induced calculi. Cases of sulfonamide urolithiasis occurring in patients with known stone disease have rarely been reported. We report a case of a patient with a brief history of recurrent calcium oxalate nephrolithiasis requiring 2 ureteroscopic procedures whose existing 6 mm lower pole renal stone more than quadrupled in size to form a 4 cm renal staghorn after 4 months of high-dose treatment for Nocardia pneumonia with trimethoprim-sulfamethoxazole. After ureteroscopy with laser lithotripsy and basketing of fragments, the stone was found to be predominantly composed of N4-acetyl-sulfamethoxazole, a metabolite of sulfamethoxazole. Stones composed of sulfamethoxazole or its metabolites are rare but have known associated risk factors that should be considered when prescribing this antibiotic. This case report illustrates additional risk factors for consideration, including pre-existing urinary calculi that may serve as a nidus for sulfamethoxazole deposition, and reviews treatment and prevention methods.

The impact of heat on kidney stone presentations in South Carolina under two climate change scenarios

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The risk of kidney stone presentations increases after hot days, likely due to greater insensible water losses resulting in more concentrated urine and altered urinary flow. It is thus expected that higher temperatures from climate change will increase the global prevalence of kidney stones if no adaptation measures are put in place. This study aims to quantify the impact of heat on kidney stone presentations through 2089, using South Carolina as a model state. We used a time series analysis of historical kidney stone presentations (1997-2014) and distributed lag non-linear models to estimate the temperature dependence of kidney stone presentations, and then quantified the projected impact of climate change on future heat-related kidney stone presentations using daily projections of wet-bulb temperatures to 2089, assuming no adaptation or demographic changes. Two climate change models were considered-one assuming aggressive reduction in greenhouse gas emissions (RCP 4.5) and one representing uninibited greenhouse gas emissions (RCP 8.5). The estimated total statewide kidney stone presentations attributable to heat are projected to increase by 2.2% in RCP 4.5 and 3.9% in RCP 8.5 by 2085-89 (vs. 2010-2014), with an associated total excess cost of ~ $57 million and ~ $99 million, respectively.

- Jennifer Allmaras, MPH, 1/25/2022

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