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CLINICAL PHENOTYPING FOR PAIN MECHANISMS IN UROLOGIC CHRONIC PELVIC PAIN SYNDROMES: A MAPP RESEARCH NETWORK STUDY

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Abstract

Three categories of pain mechanisms are recognized as contributing to pain perception: nociceptive, neuropathic, and nociplastic (i.e., central nervous system augmented pain processing). We use validated questionnaires to identify pain mechanisms in Urologic Chronic Pelvic Pain Syndrome (UCCPS) patients (n=568, female=378, male= 190) taking part in the Symptom Patterns Study of the Multidisciplinary Approach to the study of chronic Pelvic Pain Research Network.

A cutoff score of 12 on the painDETECT questionnaire (−1–38) was used to classify patients into the neuropathic category while the median score of 7 on the fibromyalgia survey criteria (0–31) was used to classify patients into the nociplastic category. Categories were compared on demographic, clinical, psychosocial, psychophysical and medication variables.

At baseline, 43% of UCPPS patients were classified as nociceptive-only, 8% as neuropathic only, 27% as nociceptive+nociplastic, and 22% as neuropathic+nociplastic. Across outcomes nociceptive-only patients had the least severe symptoms and neuropathic+nociplastic patients the most severe. Neuropathic pain was associated with genital pain/sensitivity on pelvic exam, while nociplastic pain was associated with comorbid pain conditions, psychosocial difficulties, and increased pressure pain sensitivity outside the pelvis.

A self-report method classifying individuals on pain mechanisms reveals clinical differences that could inform clinical trials and novel targets for treatment.

Introduction

Two conditions characterized by chronic pelvic pain, interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) are highly prevalent and characterized by chronic and often debilitating pain in the pelvic region and/or genitalia, along with a spectrum of bladder and lower urinary tract symptoms.[1, 2] These conditions, that are together referred to as Urologic Chronic Pelvic Pain Syndrome (UCPPS), have been historically poorly understood and show only modest improvement from traditional treatments. To better understand the etiology and how best to treat UCPPS, the NIDDK/NIH established the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network (http://www.mappnetwork.org/).[3, 4] One approach for learning more about UCPPS has been to characterize subgroups of individuals with UCPPS based upon self-reported features of different pain mechanism categories.

The International Association for the Study of Pain (IASP) has defined three such mechanisms of pain while recognizing that more than one mechanism may be operative in any given patient. [5, 6] These are: *Nociceptive pain* arising from activation of nociceptors in non-neural tissue (e.g., either musculoskeletal and/or inflammatory); *Neuropathic pain* resulting from lesions to the somatosensory nervous system (i.e., either peripheral or central depending upon the site of the lesion)[7]; and *Nociplastic pain*, associated with the process

of central sensitization, referring to alterations in how sensory input gets processed in the brain as pain.[5, 7, 8] Historically, the conditions defined by UCPPS have been assumed to be inflammatory in nature (e.g., interstitial cystitis with Hunner's lesions, chronic prostatitis) but often fail to respond to treatments directed towards local inflammatory processes.[9] Several studies have confirmed that only a small proportion of patients with UCPPS, whether IC/BPS or CP/CPPS, show evidence of inflammation on exam/biopsy, supporting the need to explore additional pain mechanisms.[10–12]

Despite having a UCPPS diagnosis, the actual clinical course and treatment response for any given individual may depend heavily upon which pain mechanism is influencing the symptomatology. In research settings, subtyping individuals based upon pain mechanisms often uses resource-intensive approaches such as quantitative sensory testing (QST) and/or neuroimaging.[13, 14] Recently, survey methodology, more amenable to the clinical setting, has been developed that can estimate the likely mechanism of pain for a given individual. [15–20] This approach has not yet been applied to UCPPS, despite broad recognition of the heterogeneous nature of the underlying conditions.

In this study, we used data from the MAPP research network to address the following questions: (1) Is UCPPS predominantly a nociceptive pain condition, or do other pain mechanisms contribute? and (2) if more than one mechanism is represented in UCPPS, can clinically meaningful mechanism-based phenotypes of UCPPS be identified with distinct risk factors and consequent treatment implications?

Methods

Participants

MAPP-II participants with UCPPS in the Symptom Patterns Study (SPS) who completed the patient-reported outcome measures (PROMs) for assessment of pain mechanisms (n=568) were included as well as pain-free community controls for psychophysical pain testing (n=72). The scientific aims of the Network, recruitment strategy, and inclusion and exclusion criteria have been described in detail in a recent publication.[21] The MAPP-II project is registered at Clinicaltrials.gov: Trans-MAPP Symptom Patterns Study (MAPP II SPS [NCT02514265]): and is a longitudinal, observational study of the treated natural history of UCPPS. All procedures were approved by Institutional Review Boards at the participating institutions and all subjects provided informed consent.

Study Design

This retrospective analysis used existing MAPP baseline patient reported outcome data to derive subgroupings based upon PROMs that assess different pain mechanisms. The subgroupings were then compared against each other on measures of demographics, clinical characteristics, psychosocial factors, psychophysical outcomes, and medication use.

Measures

Pain Mechanisms

Pain Mechanism Classifier: Neuropathic Pain using the painDETECT: Neuropathic pain was assessed using the painDETECT questionnaire (PD-Q), a 13-item screening survey designed to identify the presence of neuropathic pain.[22] The PD-Q assesses current average and worst pain intensity over the past 4 weeks (rated on an 11-point numeric rating scale of 0–10) as well as the presence of neuropathic pain qualities (e.g. burning sensation, tingling/prickling sensations; rated on a rating scale from 0 [never] to 5 [very strongly]). Pain duration/pattern and radiation of pain are also assessed. The total score ranges from −1 to 38, with higher scores indicative of higher likelihood of neuropathic pain origin. Scores 12 indicate that a neuropathic component of pain is unlikely and suggestive of a predominant nociceptive origin, scores 13 and above indicate possible neuropathic pain with higher scores adding greater confidence. We retained the PD-Q convention wherein scores 12 were indicative of predominantly nociceptive pain and adopted 13 and above as indicating possible/likely neuropathic pain. The PD-Q was initially validated in a sample of low back pain patients but has not been specifically validated in urologic chronic pelvic pain, so we modified the question stem for the MAPP-SPS to refer to pelvic pain, e.g., "Mark the picture that best describes the course of your pelvic pain."

Pain Mechanism Classifier: Nociplastic Pain Using the Fibromyalgia Survey Criteria: The American College of Rheumatology 2016 Fibromyalgia (FM) Survey Criteria[23] combines an index assessing the number of painful body sites (i.e., the Widespread Pain Index (WPI)) with a symptom severity score (SSS) that measures symptoms such as problems thinking, fatigue, and sleep difficulties (0–12). For this study, the WPI was operationalized using the Michigan Body Map (0–19).[24] The WPI and the SSS are combined to form a continuous measure of nociplastic pain characteristics (ranging between 0–31).[23] Together, these indices capture both the extent of widespread pain and comorbid constitutional symptoms as a proxy for nociplastic pain as previous research has shown that distinguishing putative nociplastic pain patients from those with nociceptive pain is best accomplished by incorporating both aspects. Based upon our previous factor analytic work, we have shown distinct symptom groups analogous to these two subscales.[25, 26] Elevated scores on this measure, whether or not they reach epidemiologic criteria for FM, have been shown to correspond to altered central pain processing and poorer responses to peripherally directed treatments,[18, 20, 27] and is a robust predictor of both central sensitization and disability.[28–30] For this study, we adopted the median score for the sample (7) as the cut-point for classifying possible/likely nociplastic pain.

Demographic Information—Demographic information such as patient age and gender were captured by self-report.

UCPPS Clinical Measures—The 5-item RAND Interstitial Cystitis Epidemiology (RICE) case definition questionnaire was designed for epidemiological studies to identify the presence of IC/BPS symptoms in men and women. We used this measure to identify sub-groups with or without painful bladder filling and/or painful urgency.[31] Overall genitourinary pain and urinary symptoms were assessed using two measures derived from

a factor analysis of symptom data collected in the MAPP research network.[26] The pain measure is a 0–28 scale with greater pain being associated with higher scores, and the measure of urinary symptom severity (primarily increased urinary frequency) is a 0–25 scale again with greater severity being associated with higher scores.

Pelvic Examination and Genital Pain—A standardized pelvic examination was performed by experienced clinicians assessing pain in eight distinct locations: suprapubic, perineal, bilateral posterior levator muscles, bilateral obturator internus muscles, and bilateral anterior levator muscles. Patients also reported whether the examination reproduced their UCPPS pain and discomfort. The number of painful pelvic floor sites (out of 6) were summed to create a pelvic floor pain index, while perineal pain, suprapubic pain, and pain recapitulation by exam were considered separately.

Patients reported genital pain by marking pain locations on a customized genital map. For male patients the four regions were the glans penis, the penis, testicles and perineum. For females the regions included the labia, urethra, vagina and perineum. These were subsequently summed into a genital map pain score.

Comorbid Pain and Overall Pain—Non-pelvic pain intensity was assessed by a single item from the Symptom and Health Care Utilization Questionnaire (SYM-Q) on a scale of 0–10 with higher values indicative of more pain intensity.[4] Presence of five chronic overlapping pain conditions (COPCs) were assessed (irritable bowel syndrome, temporomandibular disorder, migraine headache, fibromyalgia, and myalgic encephalomyelitis/chronic fatigue syndrome) using the Complex Multi- Symptom Inventory (CMSI), a symptom checklist with follow-up standardized diagnostic modules for each condition.[32] The Brief Pain Inventory (BPI) is a 15-item self-report measure that has been validated for use in a wide variety of pain conditions. The BPI assesses for the presence of pain, pain intensity (worse, least, average, current), and functional interference from pain. Clinical pain intensity and interference were assessed using the BPI. The BPI asks about overall pain intensity/interference, and does not distinguish between pelvic and non-pelvic pain.

Psychosocial Measures—The SF-12 is a 12-item measure of functional status and generic quality of life that provides composite summary scores for physical health and mental health functioning.[33] Pain catastrophizing was assessed using the 6-item Catastrophizing sub-scale from the Coping Strategies Questionnaire (CSQ).[34] Depressive and anxiety-related symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS).[35] The HADS is a 14-item questionnaire for depression and anxiety, developed for use in non-psychiatric settings. Disability was assessed using the World Health Organization Disability Assessment Schedule (DAS 2.0).[36]

Medication Usage—Current medication use was assessed by patient self-report using a standardized concomitant medication form. The form included the name of the medication, frequency, and unit of dose.

Pressure Pain Sensitivity—Segmental mechanical sensitivity is assessed following a method modified from Lai et al.[37] A handheld, analog algometer with a 1 cm^2 flat rubber probe (FPK Algometer, Wagner Instruments, Greenwich, CT) was used to deliver quantifiable pressure stimuli to the area just beneath the umbilicus superior to the bladder. Algometry was also performed at a non-symptomatic control site on the volar forearm midway between the wrist and elbow on the dominant body side. Fixed intensity pressures (2 kg/cm^2, 5-s duration, 20-s inter-stimulus interval) were applied, 3 times each, first to the forearm control site and then to the suprapubic test site, with the participant in the supine position. Pressure was increased at rate of approximately 0.5 kg/cm^2/s . A ticking 1 Hz frequency metronome (Korg MA-1) with earphones was used by examiners to help control the rate of applied pressure and to reduce inter- and intra-examiner variability.[44] Subjects verbally rate the pain intensity of each pressure using a 0–100 NRS. The mean of three NRS ratings were used for analysis. Box-Cox transformations were applied to non-normal data for use in parametric statistics.

Statistical Analysis

Four subgroups were derived from the pain mechanism classifiers (described above). The resulting groups were the following: (1) predominant nociceptive (NOC; PD-Q 12 & FM<7), (2) predominant neuropathic (NP; PD-Q>12 & FM<7), (3) nociceptive + nociplastic features (NOC + CNS; PD-Q < 12 & FM 7), and (4) neuropathic+ nociplastic features (NP + CNS; PD-Q >12 & FM>7). Hereafter, we use these abbreviations to refer to the four groupings.

All analyses were conducted using baseline pain mechanism categorization as the independent variable. We then compared differences on demographic and clinical characteristics across the four categories using *Analysis of Variance*s and χ2 tests for continuous and categorical variables, respectively. Pairwise contrasts were between the four categories. Where data analysis is exploratory, as in the current study, corrections for multiple comparisons are generally not needed.[38] However, in recognition of the potential for familywise Type I errors, we corrected p-values for the six major clinical and symptom domains being explored (i.e., demographics, UCPPS clinical characteristics, non-pelvic pain, pelvic floor tenderness/genital pain, psychosocial/quality of life, and medication use). This more stringent level of significance, p<.0083, corresponds to adjusting the level of significance of 0.05 by a factor of six. We retained this level of significance for the separate outcomes related to psychophysical testing as well.

Results

Sample Characteristics

The baseline MAPP-II demographic characteristics have been reported elsewhere.[21] The mean age of this sample was 44.87 years (SD=15.68) and 67% were female. Overall, 70% of patients carried a diagnosis of IC/BPS, 22% CP/CPPS, 5% both, and 2% neither formal diagnosis but met minimum MAPP entry criteria. The mean age of the control sample was 41.05 years (SD=14.76) and 48.6% were female.

Distribution of Pain Mechanism Subtypes

All data are shown in Table 1 and Figure 1 presents the effect sizes of subgroup contrasts. The NOC group consisted of 246 patients or 43% of the total sample. The NP group consisted of 44 patients or 8% of the sample. The NOC+CNS group consisted of 155 patients or 27% of the sample. The NP+CNS group consisted of 123 patients or 22% of the sample. There were 167 patients or 29% of the sample who had neuropathic pain (i.e., the NP and NP+CNS groups combined) and 278 patients or 49% of the sample had nociplastic pain (i.e., the NOC+CNS and NP+CNS groups combined). Female patients were more likely to belong to NOC + CNS and NP + CNS groups than male patients.

Findings by Pain Mechanism Grouping

Nociceptive.—NOC patients reported less overall pain during pelvic exam and were least likely to report suprapubic pain on exam. NOC patients also had lower overall pain severity and interference scores than any other group. (see Table 1).

Neuropathic.—The NP group had higher levels of genitourinary pain severity than the NOC group and NOC + CNS groups, but not statistically different form the NP+CNS group. The same was true for the number of painful sites endorsed on the genital map. The NP group was also more likely to experience perineal pain on exam and to report that cardinal pain symptoms were reproduced by the exam when compared to the NOC and NOC+CNS groups, but not to the NP+CNS group. (see Table 1).

Nociceptive/Nociplastic.—The NOC+CNS group consisted of a higher proportion of female patients and patients with an IC/BPS diagnosis than the NOC and NP groups, but not the NP+CNS group. Painful bladder filling, and the presence of either or both painful filling and painful urgency, were more common in the NOC+CNS group than in the NOC group, but did not differ from the NP or NP+CNS groups. There was more non-urologic pain, COPCs, and depression reported by the NOC+CNS group when compared to the NOC and NP groups. (see Table 1).

Neuropathic/Nociplastic.—The NP+CNS group had higher urinary symptom severity than all other groups. Similarly, they had higher levels of anxiety, pain catastrophizing, and disability than all other groups, and the lowest scores for physical and mental well-being. The NP+CNS also was more likely to be using opioids than the NOC group, and used more medications in general than the NOC and NP groups. (See Table 1).

Pressure Pain Sensitivity.—Compared to controls, each pain mechanism category showed greater pressure pain sensitivity at the suprapubic site (all $p < .0083$), and the NP+CNS category showed greater sensitivity than both the NOC and NOC + CNS groups. Conversely, at the forearm, only the NOC + CNS and NP+CNS groups showed more sensitivity than controls (both $p < .0083$). Additionally, the NP+CNS group showed greater sensitivity than the NOC group ($p < .0083$). See Table 2.

Summary

Figure 2 presents a summary of findings. NOC patients generally displayed the least severe symptoms and NP+CNS patients displayed the most severe symptoms. NP patients showed high levels of pelvic pain, genital pain, and pain on pelvic exam. NOC+CNS patients had high levels of non-urologic pain and were more likely to experience painful bladder filling. NP+CNS patients had more psychosocial issues (anxiety, pain catastrophizing), lower quality of life, and greater psychophysical sensitivity outside the pelvis.

Discussion

This is the first study to examine categorical pain mechanism phenotypes in UCPPS. The results demonstrate that despite being typically considered a nociceptive/inflammatory pain condition, both neuropathic and nociplastic pain characteristics are common in UCCPS, with approximately 56% showing features of one or both. Additionally, the presence of these mechanisms is strongly associated with worse disability and quality of life, different patterns of medication usage, and differences in the presentation of symptoms. Critically, it is possible to assess these mechanisms with simple, validated, and reasonably brief self-reported measures allowing for more precision in clinical care and treatment planning. Additionally, through the use of psychophysical pain testing we were able to provide neurobiological support for these categories.

Nociplastic pain, (sometimes referred to as "centralized pain") has an established set of characteristics that were largely confirmed in the current study.[39] Nociplastic pain primarily refers to central nervous system augmentation of nociceptive input or peripheral neuropathy in the development and maintenance of chronic pain, often to such a degree that peripheral pathology may be wholly absent. In studies of fibromyalgia, the prototypical nociplastic pain condition, women are more likely to be affected and are more likely to have experienced pain early in life.[40] In the current study we found that women were more likely to have nociplastic pain and were younger than those with nociceptive pain-only. Additionally, those with nociplastic pain were more likely to have another comorbid pain condition and to have more severe non-pelvic pain, consistent with a pain mechanism that promotes global sensitivity to pain, as expected.[41] These findings echo previous reports that nociplastic pain is strongly associated with chronic overlapping pain conditions in UCPPS.[26] Patients with nociplastic pain were also more likely to report pain during bladder filling and painful urgency than those with nociceptive pain. In a previous MAPP network study it was shown that painful filling and urgency may represent more severe subtypes of UCPPS and are associated with a greater number of somatic/interoceptive symptoms in non-pelvic areas.[42] This in turn suggests the systemic amplification of sensory signals as a component of nociplastic pain in UCPPS.[26, 39, 43] This basic concept found support in the results of our psychophysical pain testing protocol – although all patient subtypes were more sensitive than controls at the pubic area, only patients with a nociplastic pain component showed forearm sensitivity, as would be expected in a nociplastic group. Taken together, these findings suggest that treatments designed to address central amplification could be useful in patients when nociplastic pain is present, such as

low-dose tricyclic compounds or non-pharmacologic therapies such as cognitive behavioral therapy.[44]

Neuropathic pain was strongly associated with more severe and less focal pelvic pain locations. Overall genitourinary pain severity and the number of genital areas endorsed as painful were greater in those with neuropathic pain than in those with nociceptive pain or nociplastic pain in the absence of neuropathic pain. These findings were supported by pelvic exam findings, where pelvic floor tenderness was more common in those with neuropathic pain than in those with nociceptive or nociplastic pain only. These findings generally support the view that regional or pelvic sensitization (i.e., genital pain or pelvic floor pain) is a feature of neuropathic pain in UCPPS. Together these findings suggest that treatments targeting pelvic pain sensitization are likely to be most helpful in patients with neuropathic pain, such as local nerve blocks.[45]

Patients with both neuropathic and nociplastic pain generally experienced the worst symptoms of any group, and especially when compared to those with nociceptive pain only. Having both neuropathic and nociplastic pain present in the same individual appeared to result in the greatest decrements in quality of life and more disability than would be expected by the presence of either mechanism alone. Pain interference, disability, and psychosocial issues were greatly elevated in this group. Notably, this group had the youngest average age of all four phenotypes, in addition to the greatest disability. Pain mechanisms are thought to be interactive,[8] and for this grouping, the combination is particularly debilitating. Although nociplastic pain can initiate and maintain pain in some cases with little ongoing peripheral pathology or nociceptive input, patients with nociplastic pain report more pain in response to the same standardized experimental pain paradigms as individuals without nociplastic pain.[46] Thus, patients with nociplastic pain are likely to experience more pain in response to both peripheral nociceptive and neuropathic input than those without. Clinically, the presence of this combination suggests the need for a multi-pronged treatment approach that can treat the central and peripheral aspects of the disorder simultaneously.

Medication usage also showed strong differences between groups, and suggested that tailoring of treatment to pain mechanisms could be greatly improved in UCPPS. Those with both neuropathic and nociplastic pain features were the most likely to be currently using opioids than those with nociceptive pain, despite the fact that opioids appear to be less effective in those with nociplastic pain features.[47] Conversely, there were no differences in the use of peripherally directed or (non-opioid) centrally acting treatments by treatment groups. This likely represents an area of needed improvement in clinical care for UCPPS.

There are several strengths and weaknesses associated with the current study. The sample size is large and is a good representation of the diversity of clinical presentation seen in UCPPS. The PROMs used in this study were validated and relatively easy to administer, easing the translation of their use from a research setting to clinical practice. The comprehensive nature of assessment in the MAPP research network allowed us to examine several important domains, ranging from pelvic exam to patterns of medication usage. One weakness of the current study is that nociceptive pain is, by convention of

the painDETECT, a classification of exclusion. A large proportion of the sample (43%) did not have neuropathic or nociplastic pain by the adopted criteria, but no assessment of peripheral inflammation by exam or biopsy was conducted. Thus, patients without neuropathic or nociplastic pain require further characterization. These pain mechanisms exist on a continuum and may overlap, and so the current approach is a simplification, but a necessary one for categorical clinical classification. Some aspects of this study should be considered exploratory. Our classifications based on median splits within our sample need to be examined for external validity (i.e., whether the categorization is related to other clinical outcomes in other samples). The lack of validation of the painDETECT in urologic pelvic pain samples is a distinct limitation, in that the neuropathic pain qualities affirmed by the patients cannot be tied to gold-standard diagnostic procedures as in the original study. We altered some of the question stems of the painDETECT to refer directly to pelvic pain – this approach represented a modification to the standard administration of this instrument, and the cutoff criteria were adopted from the original publication. Although the FM survey criteria is a promising proxy for nociplastic pain, this pain mechanism is still an emerging construct and so the method of assessment and cutoff decisions may continue to evolve. These limitations will be important to address in future studies as the investigated phenotypes are developed further.

Conclusions and Future Directions

Pain mechanisms can be assessed with self-report measures in UCPPS and show large clinically relevant differences between the resulting groups. Pathophysiological validation of the subgroups and adjustment of cut-points to UCPPS may strengthen the utility of these instruments. Clinical trials designed to test precision medicine hypotheses in UCPPS related to pain mechanisms are a natural extension of this work.

Acknowledgements

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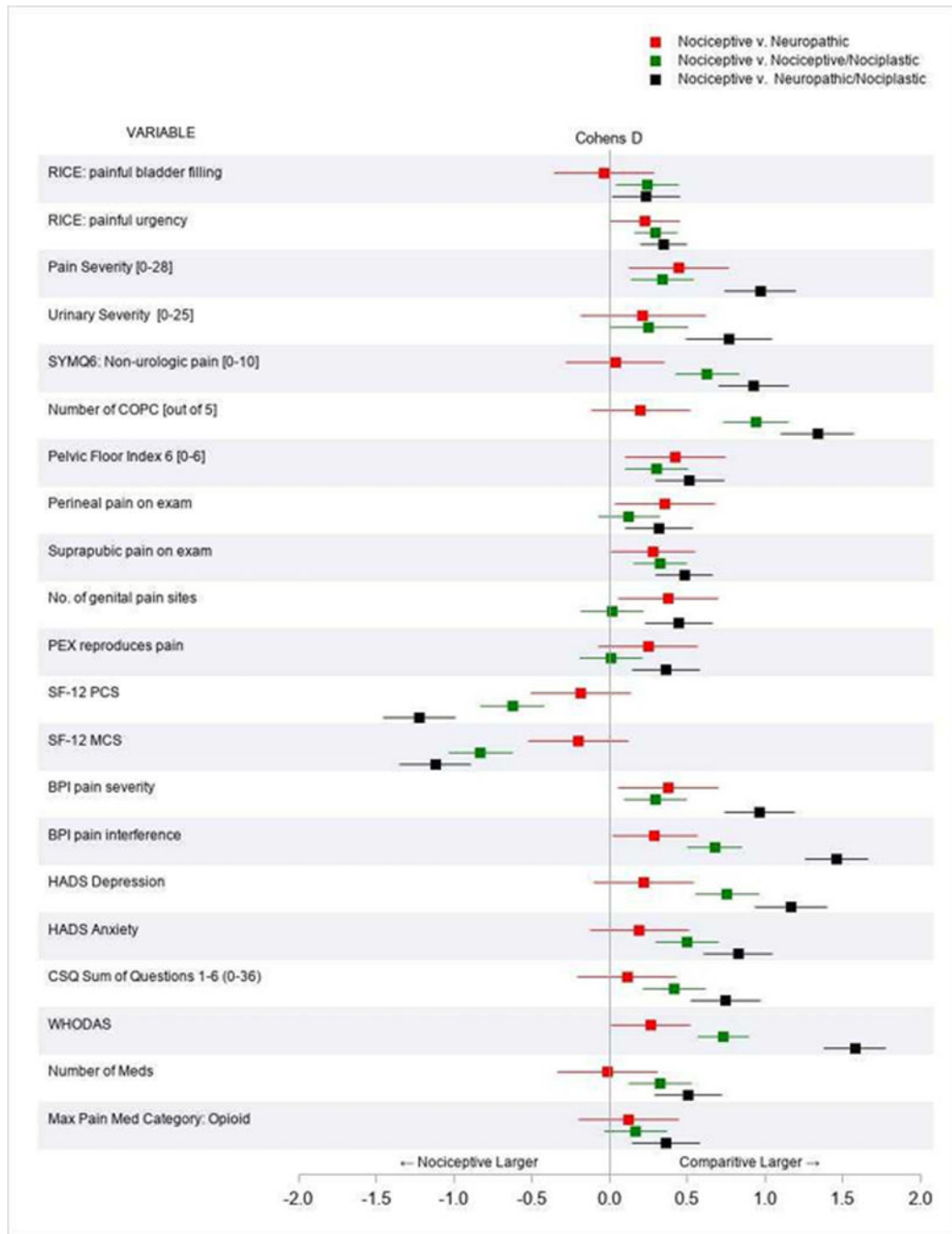
Figure 1.
Cohen's d effect sizes and associated confidence intervals (adjusted to p=.0083 for study measures between Neuropathic, Nociplastic, and Neuropathic/Nociplastic groups compared to the Nociceptive group.
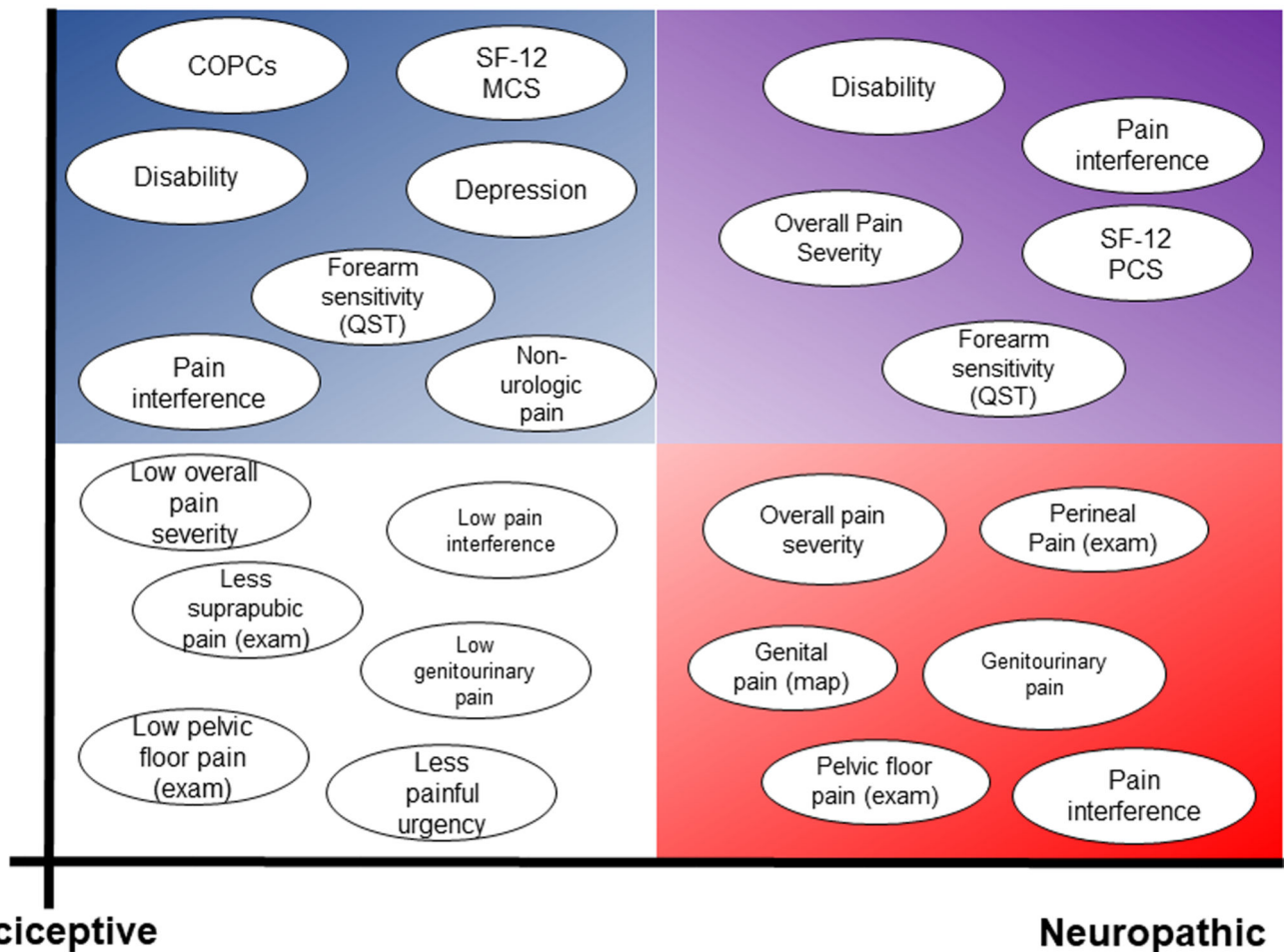
Figure 2.
Summary of major findings. The Nociceptive square shows symptom measures that were significantly lower in this group compared to each of the other three groups. The Nociplastic and Neuropathic squares show the six symptom/clinical measures that were largest for these groups by Cohen's d effect size when compared to the Nociceptive group. The Neuropathic + Nociplastic square shows symptom/clinical measures whose Cohen's d effect size 95% CI (compared to Nociceptive) exceeded the same 95% CIs for the Neuropathic and Nociplastic groups.

Table 1.

Demographic and Clincial Characteristics of Pain Mechanism Groups

Variable	Stat	Nociceptive	Neuropathic	Nociceptive/Nociplastic	Neuropathic/Nociplastic	p-value*
Participants	Sum	246	44	155	123	-
DEMO						
Age	Mean (SD)	47.6 (16.32) [b]	45.1 (15.39) [ab]	43.4 (15.62) [ab]	41.3 (13.63) [b]	0.0016
Sex	Male	106 (43.1%)	19 (43.2%)	37 (23.9%)	28 (22.8%)	<.0001
Sex	Female	140 (56.9%)	25 (56.8%)	118 (76.1%)	95 (77.2%)	
UCPPS Clinical characteristics						
Diagnosis	IC/BPS	155 (63.0%) [c,d]	27 (61.4%)	122 (78.7%)	96 (78.0%)	0.0100
Diagnosis	CP/CPPS	70 (28.5%)	12 (27.3%)	27 (17.4%)	16 (13.0%)	
Diagnosis	Both	16 (6.5%)	4 (9.1%)	6 (3.9%)	8 (6.5%)	
Diagnosis	None	5 (2.0%)	1 (2.3%)	0 (0%)	3 (2.4%)	
RICE: painful bladder filling	Yes	143 (58.1%) [c,d]	24 (54.5%)	112 (72.3%)	90 (73.2%)	0.0024
RICE: painful urgency	Yes	141 (57.3%) [b,c,d]	35 (79.5%)	116 (74.8%)	98 (79.7%)	<.0001
RICE: Either	Yes	187 (76.0%) [c,d]	38 (86.4%)	140 (90.3%)	111 (90.2%)	0.0002
RICE: Both	Yes	97 (39.4%) [c,d]	21 (47.7%)	88 (56.8%)	77 (62.6%)	<.0001
Symptom Duration (years)	Mean (SD)	11.5 (11.76)	9.4 (9.58)	13.1 (12.36)	13.4 (11.33)	0.1335
Pain Severity [0–28]	Mean (SD)	12.0 (5.45) [b,c,d]	16.4 (4.37)	14.1 (4.83) [b,d]	18.4 (4.71) [a]	<.0001
Urinary Severity [0–25]	Mean (SD)	9.7 (6.01)	12.1 (5.99)	11.5 (5.65)	15.6 (5.66) [a,b,c]	<.0001
Comorbid Pain						
SYMQ6: Non-urologic pain [0–10]	Mean (SD)	2.3 (2.25)	2.5 (2.30)	4.1 (2.37) [a,b]	5.2 (2.58) [a,b,c]	<.0001
Number of COPC [out of 5]	Mean (SD)	0.4 (0.65)	0.8 (0.94)	1.5 (1.17) [a,b]	2.1 (1.32) [a,b,c]	<.0001
Pelvic floor and genital map						
Pelvic Floor Index 6 [0–6]	Mean (SD)	2.9 (2.04) [b,c,d]	4.5 (1.73)	3.7 (2.01)	4.3 (1.83)	<.0001
Perineal pain on exam	Yes	50 (20.7%) [c,d]	22 (52.4%) [c]	40 (27.0%) [d]	47 (39.2%)	<.0001
Suprapubic pain on exam	Yes	86 (35.5%) [b,c,d]	26 (63.4%)	82 (55.4%)	81 (67.5%)	<.0001
no. of genital pain sites on sex-specific genital map	Mean (SD)	1.2 (1.07) [b,d]	2.0 (1.18) [c]	1.2 (1.05) [d]	1.8 (1.18)	<.0001
PEX reproduces pain	1 = Yes	139 (58.4%) [b,d]	34 (82.9%) [c]	86 (58.9%) [d]	97 (81.5%)	<.0001

Variable	Stat	Nociceptive	Neuropathic	Nociceptive/Nociplastic	Neuropathic/Nociplastic	p-value*
Psychosocial and QOLI						
SF-12 PCS	Mean (SD)	50.5 (7.81) [c,d]	47.4 (7.31) [d]	44.1 (9.29) [d]	36.9 (9.15)	<.0001
SF-12 MCS	Mean (SD)	49.0 (8.55) [c,d]	45.4 (7.53) [c,d]	39.7 (9.82) [d]	35.4 (10.15)	<.0001
BPI pain severity	Mean (SD)	11.9 (7.47) [b,c,d]	17.3 (6.96) [d]	14.5 (7.11) [d]	21.1 (7.42)	<.0001
BPI pain interference	Mean (SD)	14.0 (12.96) [b,c,d]	22.3 (15.82) [d]	26.1 (15.33) [d]	42.2 (16.76)	<.0001
HADS Depression	Mean (SD)	3.4 (3.23) [c,d]	5.0 (3.52) [c,d]	6.9 (4.17) [d]	9.3 (4.69)	<.0001
HADS Anxiety	Mean (SD)	5.5 (3.97) [d]	7.1 (3.97) [d]	8.1 (4.62) [d]	10.2 (5.11)	<.0001
CSQ Sum of Questions 1–6 (0–36)	Mean (SD)	8.5 (7.43) [c,d]	10.2 (7.61) [d]	12.5 (7.96) [d]	16.3 (9.06)	<.0001
WHODAS	Mean (SD)	5.59 (5.74) [b,c,d]	9.25 (16.54) [d]	11.81 (7.19) [d]	20.02 (8.95)	<.0001
Medication Use						
Number of Meds	Mean (SD)	6.4 (4.45) [c,d]	6.3 (3.64) [d]	8.4 (5.32) [d]	9.8 (6.65)	<.0001
Max Pain Med Category	None	59 (24.0%)	10 (22.7%)	26 (16.8%)	17 (13.8%)	0.0142
Max Pain Med Category	Peripheral	48 (19.5%)	8 (18.2%)	31 (20.0%)	21 (17.1%)	
Max Pain Med Category	Central	109 (44.3%)	17 (38.6%)	68 (43.9%)	48 (39.0%)	
Max Pain Med Category	Opioid	30 (12.2%) [b]	9 (20.5%) [ab]	30 (19.4%) [ab]	37 (30.1%) [a]	

[a] p < .0083 vs. NOC

[b] p < .0083 vs. NP

[c] p < .0083 vs. NOC + CNS

[d] p < .0083 vs. NP + CNS

Table 2.

Pressure pain sensitivity for pain mechanism subgroups and controls.

Phenotype Category	Average Pain Rating (pubic)	ll	ul	Average Pain Rating (forearm)	ll	ul
Nociceptive	8.35^a	6.23	10.98	4.65	3.21	6.52
Neuropathic	13.66 ^{a}	7.26	23.57	6.35	2.72	12.80
Nocicpetive/Nociplastic	11.67 ^{a}	8.29	16.00	6.94^a	4.54	10.17
Neuropathic/Nociplastic	19.76 ^{a,b,c}	14.11	26.95	8.58^{a,b}	5.48	12.85
Controls	2.75	1.30	5.17	2.46	1.06	4.93

[a] p < .0083 vs. controls

[b] p <.0083 vs. nociceptive

[c] p < .0083 vs. nociceptive/nociplastic