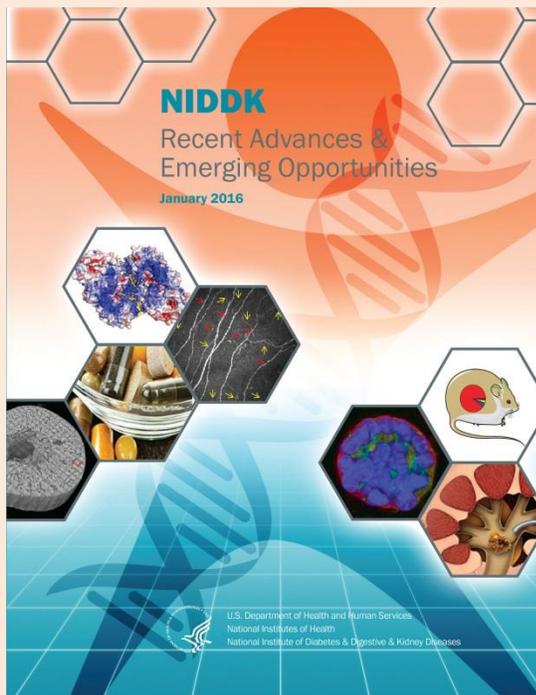


The Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network: Yielding New Insights into Challenging Urologic Pain Syndromes

A feature excerpted from *NIDDK Recent Advances & Emerging Opportunities 2016*

The following feature, published in January 2016 as part of a larger document (see below), describes the background, goals, and novel approaches of the MAPP Research Network, which is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). It also summarizes just some of the fascinating findings that have emerged from the first phase of the Network—findings made possible by the combined efforts of Network scientists, clinicians, and participants. It concludes by looking forward to how these and other findings, as well as ongoing efforts, may ultimately help benefit people living with urologic chronic pelvic pain syndromes.

NIDDK Recent Advances & Emerging Opportunities:



NIDDK Recent Advances & Emerging Opportunities is a publication that the NIDDK has issued annually since 2001. Written for the general public, it is a compendium that highlights examples of the many research advances published by NIDDK-funded scientists and their colleagues in the most recent fiscal year, along with the technologies that made these achievements possible. In addition to research advances, the compendium includes:

- "Stories of Discovery," which trace research progress in specific areas over a much longer period of time;
- "Scientific Presentations," which have been made by eminent researchers during 2015; and
- "Patient Profiles," which recount the personal stories of several patients whose lives have been adversely affected by disease.

This publication is one means of conveying the important accomplishments that have resulted from NIDDK-funded research, as well as the enormous promise this research holds for the future. The examples provided are representative of the much larger and more diverse research portfolio funded by the NIDDK. This compendium is a web-based publication, which is also presented to the NIDDK's National Advisory Council in printed form each January or February. To view and download the full 2016 edition of the publication, please go to: <http://www.niddk.nih.gov/about-niddk/strategic-plans-reports/Pages/NIDDK-recent-advances-emerging-opportunities-2016.aspx>



The Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network: Yielding New Insights into Challenging Urologic Pain Syndromes

Chronic, often debilitating pain in the pelvic or genital areas, frequently accompanied by urinary symptoms such as needing “to go” urgently or many times a day: These are hallmark symptoms of urologic chronic pelvic pain syndrome (UCPPS), a term that encompasses both interstitial cystitis/bladder pain syndrome (IC/BPS, also called IC/painful bladder syndrome (PBS)), which predominantly affects women, and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), which affects men. These pain conditions reduce quality of life and productivity and incur significant health care costs for millions of Americans.

Despite many years of committed basic and clinical research efforts supported by the NIDDK and other research funding agencies, the cause(s) of UCPPS has long remained elusive, as have widely or fully effective treatments. Moreover, diagnostic tests are not currently available. Instead, because many UCPPS symptoms can be suggestive of known diseases, those diseases need to be ruled out first—making IC/BPS or CP/CPPS a “diagnosis of exclusion.” While public and clinical awareness of UCPPS is increasing due to educational efforts by the NIDDK and major health advocacy organizations, such as the Interstitial Cystitis Association and the Prostatitis Foundation, many people suffer

for years with symptoms and no diagnosis. In the face of these challenges, discoveries emerging from the NIDDK-sponsored Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network are bringing scientists and clinicians closer to understanding the cause(s) of UCPPS, improved diagnosis, better characterization of patients to help identify more effective treatments, and ways to prevent onset.

A New Approach

Historically, much of the NIDDK-supported research on causes and treatments for IC/BPS and CP/CPPS focused on the bladder and prostate, respectively. This was because these organs and tissues were thought to be the sites of origin for the pain and other symptoms suffered by persons diagnosed with UCPPS. Despite a broad array of studies exploring many hypotheses, however, researchers were unable to find satisfactory medical explanations for symptoms or to identify definitive risk factors or viable therapies, with the exception of a single study suggesting that myofascial physical therapy might be effective in some IC/BPS patients. At the same time, a growing body of evidence was revealing that many people with UCPPS frequently have other, overlapping chronic pain conditions, such as irritable bowel syndrome

(IBS) and fibromyalgia. Taken together, these outcomes and findings suggested that, at least in some people, UCPPS might not be a localized pain condition, but instead be part of a global pain process involving the central nervous system (*i.e.*, the brain and spinal cord) and potentially other body systems, such as the immune system. These insights also suggested that there might be a greater degree of diversity among persons grouped together under a UCPPS diagnosis than was initially thought.

In 2008, armed with these new perspectives and input from the scientific and health advocacy communities, the NIDDK launched Phase I of the MAPP Research Network. Established through a Request for Applications, this phase of the Network comprised six “Discovery Sites” at research institutions across the country, complemented by a Data Coordinating Center to manage and store clinical data and a Tissue and Technology Center to centrally process, store, and disburse clinical samples. This novel, multi-site research network embraced a unique, systemic (whole-body) approach to the study of IC/BPS and CP/CPSS to address clinically relevant questions. The Network gathered together scientists with diverse research expertise—including basic science, clinical urology, behavioral science, immunology, epidemiology, neurobiology, psychology, chronic pain, neurobiology/neuroimaging and infectious diseases—all working collaboratively to better understand UCPPS. In addition to moving beyond traditional bladder- and prostate-specific research directions to an innovative, multidisciplinary strategy for studying UCPPS, Network scientists sought to investigate potential relationships between these syndromes and the other chronic pain conditions that are often seen in people with UCPPS, such as IBS, fibromyalgia, and chronic fatigue syndrome. Thus, Network leaders included

not only urologists, but investigators specializing in these overlapping pain conditions.

Foundation Studies and Novel Findings

In Phase I, the MAPP Research Network recruited 424 men and women with UCPPS in a central, Trans-MAPP Epidemiology and Phenotyping study to better understand how these conditions progress over time (the natural history) and to learn if patients might fall into different, distinguishable subgroups based on differing symptoms that may arise from different causes—and, thus, may require different treatments. To achieve its goals, the Network also recruited “control” participants—both healthy persons without any pain syndromes (415 individuals), and those who have one or more of the overlapping chronic pain conditions (200 individuals).

The Network also conducted a number of other collaborative studies across sites complementing the central Trans-MAPP study—for example, there is evidence that alterations in the brain and spinal cord play important roles in chronic pain, so brain-imaging studies looking at structure and function were conducted across the Network using standardized protocols. Other efforts included various studies to identify biomarkers of disease, to assess the possible role of infectious agents, and to provide a systemic view of disease. The development and assessment of clinically relevant animal models of UCPPS has also been part of the Network’s efforts. In addition, individual Network sites have conducted studies to test ideas complementary to the Trans-MAPP central clinical study. Importantly, the Network was structured so that investigators would draw upon a shared pool of participant data and samples from across the Network collected using common protocols.

To establish the central Trans-MAPP study, people with IC/BPS or CP/CPPS and control participants were initially asked to fill out a number of questionnaires covering a variety of topics, including urologic pain, emotional state, other types of pain, and other symptoms and quality of life issues. They were also asked to provide blood and urine samples for use in some of the research studies. Additionally, a subset of participants engaged in a simple pressure pain threshold procedure that is a way to directly assess pain sensitivity. For participants with UCPPS, this initial, in depth clinic-based visit was followed by two additional visits at 6 and 12 months after enrollment. During that year, these participants were also registered with an Internet-based system so that they could fill out assessments of their symptoms every 2 weeks. This regular symptom assessment, a key component of the central epidemiological study, was a particularly valuable tool, as it has enabled MAPP Research Network scientists to learn a great deal about UCPPS symptoms, symptom fluctuations, and their possible correlations with other factors. The data and samples collected for the central study have also served as a crucial resource for other collaborative studies and site-specific studies in the Network.

During Phase I, the Network made significant progress on a variety of fronts, and results of Network analyses continue to emerge in scientific meetings and in peer-reviewed publications. Recent scientific reports describing novel advances in four major areas—clinical research tools, symptom flares, brain changes, and biomarkers/potential mediators—are summarized below.

Clinical Research Tools

As described previously, a large part of the central trans-MAPP study consisted of participants completing a variety of questionnaires to

describe the key symptoms of pain and bladder dysfunction, as well as issues such as depression, sleep quality, and general quality of life. While a few of these questionnaires were developed specifically for the MAPP Research Network, the majority have already been employed in health care settings and in clinical research to assess the impact of UCPPS on individuals and the outcomes of clinical trials, respectively. In the past, many of these questionnaires were used to generate a composite “score” for UCPPS that combined pain and bladder symptoms. However, a recent analysis of data from a subset of questionnaires administered in the trans-MAPP study allowed Network scientists to determine that such a composite score can “mask” independent responses in each of these areas—i.e., their analysis suggests that improvement or worsening can occur in pain independently of bladder symptoms, and vice versa, and that a composite score limits the ability of researchers and clinicians to detect such changes. In addition, they found a differential impact of these key symptoms on an important comorbidity, depression: only pain symptoms were associated with depression. These results indicate that, going forward, pain and urinary symptoms should be scored independently in UCPPS to enable more accurate research analyses and improved patient care.

Symptom Flares

People with UCPPS have reported suffering from symptom “flares”—brief or extended periods of time when symptoms intensify. Understanding flares is important both for research studies—in which flares need to be taken into account when assessing the success of a therapeutic intervention for UCPPS, for example—and also in developing clinical tools to measure and improve patient quality of life. Network scientists conducted a collaborative study at four Discovery Sites to learn

more about the impact of flares on individuals' lives, as well as gain more insight into associated triggers and treatment. The study involved eight focus groups (two groups per site) of women with IC/BPS, for a total of 57 individuals.

As a result of the moderated focus group discussions and accompanying questionnaires, the researchers found that flares were common and varied widely in their nature (e.g., pain, diarrhea, nausea), intensity (moderate to severe), frequency (daily to once a year or less), and duration (minutes to years); there were also some distinctions in frequency and duration between mild or moderate flares and the more severe flares. The most disruptive flares seemed to be those that were painful in nature, were accompanied by bladder symptoms, and lasted for days. Most participants could identify at least some of their triggers, though not all. Examples included stress, diet, allergies, medications, brand of toilet paper, and emotional state. Also, many triggers were individual specific—e.g., exercise could be a trigger in one person and a management strategy in another. Participants described approaches they used for preventing and self-managing flares but, crucially, they also conveyed the immediate and longer-term impacts of flares, from having to cancel social engagements, to living in a state of constant vigilance and anxiety (which in turn affected family and other relationships), to losing jobs and educational opportunities due to the severity of flares. The very negative impact of flares suggests that future research focused on preventing and mitigating flares would have a positive impact on quality of life for these individuals. This study also revealed how a sense of control over some aspect of symptoms (through medication or other means) is an important coping mechanism for many persons experiencing flares, especially as the unpredictability of flares is part of

their negative impact; thus, empowering patients through, e.g., discussing treatment strategies for flares, could be integrated into clinical care.

Brain Changes

Brain changes have been observed in individuals suffering from a variety of painful conditions, but identifying changes in brain structure and function in large numbers of well-characterized people with UCPPS in a standardized manner had not been attempted previously. Network scientists recently reported a variety of differences in brain structure and function between women and men with UCPPS and healthy counterparts. For example, one study focused on “white matter,” the structures that facilitate communication of information between and within brain regions. Using an imaging technique that detects a marker of white matter structural integrity, Network researchers found that, compared to healthy controls, women with IC/BPS exhibited white matter abnormalities in several different brain regions. Moreover, these alterations appear to be clinically relevant, as they correlated variously with pelvic pain severity, urologic symptoms, and quality of life as reported by participants. These results complement a prior Network study of women with IC/BPS that found that increases in pain and mood disturbance were associated with increases in the volume of “gray matter”—the brain tissues responsible for cognition, sensory perception, emotion, and muscle control, which can form connections via white matter.

Network scientists have also used a technique called functional magnetic resonance imaging (fMRI) to explore how brain regions work together to produce pain or how they may be modified in the context of chronic pain, and to possibly identify signature alterations in this “functional connectivity” germane to UCPPS. Comparing fMRI brain scanning data from 45

women with UCPPS but no comorbid conditions and 45 healthy controls, scientists found significant alterations in functional connectivity between several brain regions and networks in symptomatic women while at rest—i.e., not actively engaged in tasks. These alterations included decoupling of two brain regions from the brain's "default mode network," a pattern of brain activity that is engaged when people are involved in undisturbed, task-free, introspective thought—suggesting that persons with UCPPS may experience dysfunction in this default network. Moreover, the two decoupled regions exhibited altered functional connectivity—both increases and decreases—with other brain regions, including ones involved in pain; sensory, motor, and emotion regulation processes; reward; and higher executive functioning. These latter alterations were associated with clinical and behavioral measures reported by the participants within 48 hours of their brain scans, including pain, anxiety, and self-esteem, and may reflect a literal shift in brain focus in persons with UCPPS from introspective thought towards aspects of pain and emotion regulation.

In another study, Network scientists used fMRI to examine the relationship between chronic pain and brain involvement in pelvic floor muscle control in men with CP/CPPS. In addition to experiencing pain in this area, men with CP/CPPS are known to have abnormalities in pelvic floor muscle activity. In the study, researchers first identified in healthy men a brain region involved when actively contracting pelvic floor muscles, as well as a distinct region involved in muscle contraction in a non-painful area in men with CP/CPPS (the right hand). They then used brain scans from multiple Discovery Sites to look at the functional connectivity of these

regions in both men with CP/CPPS and healthy men while at rest to see if there were differences that could help explain the altered pelvic floor muscle activity in men with CP/CPPS. They found that, compared to functional connectivity of the hand control region, there was a significant alteration in functional connectivity of the brain region involved in pelvic muscle control in men with CP/CPPS versus healthy controls. The alteration affected functional connectivity to a brain region involved in processing and providing an emotional response to a broad spectrum of sensory inputs from the body (e.g., it is involved in experiences such as food cravings, nausea, pain, and disgust). This altered functional connectivity was significantly associated only with pain symptoms and not with other symptoms experienced by men with CP/CPPS, and the degree of alteration tracked with the severity of pain symptoms reported by participants. This study is the first to identify brain activity changes in men with CP/CPPS compared to healthy men, points to an important role for brain control of muscle activity in this disorder, and suggests a possible signature alteration that could be explored both as a biomarker of treatment success and a predictor of response to treatment.

These findings contribute significantly to the growing body of evidence for involvement of the central nervous system (CNS) in UCPPS. Importantly, as all of these studies are "snapshots" of the brain at one point in time, it remains unclear whether the structural and functional changes are causes or consequences of UCPPS. However, these findings can now be pursued to determine the potential role(s) of these differences in symptom manifestation, maintenance, and amelioration.

Biomarkers/Potential Disease Pathways

Network scientists are pursuing a variety of hypotheses and efforts to identify molecules or biological changes, or “biomarkers,” that are easily detected and consistently associated with some aspect of UCPPS. Moreover, some biomarkers for UCPPS may differ among individuals and thus could potentially distinguish subgroups of people with this condition who may benefit from different therapies. (This approach would be similar to testing for *BRCA1* gene mutations to help in selecting a specific cancer therapy.) In a recent study, scientists at a Phase I Discovery Site investigated certain inflammatory responses as potential indicators of underlying biological processes in UCPPS, and whether they are also associated with differing pain profiles in some people with UCPPS. Inflammation is a bodily process that is normally used to help defend against infection; some typical signs of inflammation are redness, heat, and pain. However, if inflammation is activated inappropriately, people can suffer needlessly from its effects, including pain. In a prior study, the research team had found that there was an association between pelvic pain symptoms in women with IC/BPS and heightened inflammatory responses mediated by two cellular proteins called toll-like receptor (TLR)-4 and TLR-2. Building on these findings, the scientists investigated whether these inflammatory responses could further differentiate between women experiencing pelvic pain and women also reporting widespread pain outside the pelvic area. The magnitude of TLR-mediated inflammatory responses can be detected in a laboratory test using blood samples. Comparing the results of blood sample tests to pain symptom data from participants at their Discovery Site, the scientists found that women with IC/BPS who had a higher than average TLR-4-mediated inflammatory response were significantly more likely to be

reporting pain symptoms outside of, as well as in, the pelvic area. As might be expected from the first finding, TLR-4-mediated inflammatory responses were also higher among women with IC/BPS who had been diagnosed with one or more overlapping pain conditions. While additional studies will be needed in a larger and more diverse sample of women, these findings suggest that the magnitude of TLR-4-mediated inflammatory responses may be a biomarker that can differentiate between subgroups of women diagnosed with IC/BPS in a way that could advance both clinical research and clinical care.

Other findings emerging from Phase I Network studies include insights into the course of UCPPS in women and men; differences between people with UCPPS and healthy controls in microbes associated with the bladder; and identification of clinical characteristics that could help differentiate potentially relevant subgroups among participants with UCPPS.

Next Steps

In light of the progress, novel findings, important new research resources, and resulting new hypotheses developed during Phase I of the MAPP Research Network, the NIDDK decided to support continuation of its efforts. With co-funding from the NIH Office of Research on Women's Health (ORWH), the NIDDK issued a second set of Requests for Applications and in FY 2014 renewed the MAPP Research Network for a second 5 year phase. In Phase II, the Network has been enhanced by the integration of three additional Discovery Sites.

As Network studies move forward, investigators are building upon Phase I discoveries and continuing efforts to provide a foundation for

effective clinical interventions for IC/BPS and CP/CPSP. For example, Network researchers are engaged in a multi-faceted Trans-MAPP Symptom Patterns Study (SPS) designed to better understand symptom change profiles over time and associated biological changes and risk factors. The SPS includes studies to help clarify whether structure and functional changes in the brain are cause or consequence of UCPPS, by looking at participant brain images over time. Other SPS studies include evaluating promising biomarkers/potential mediators identified in Phase I, and pursuing identification of UCPPS patient subgroups defined by differences in clinical symptoms and underlying biological factors. The Network is also implementing the results of the questionnaire analysis described previously to score pain and urinary symptoms separately. To better understand findings from the clinical research, Network researchers will study animal models to examine possible biological mechanisms underlying UCPPS. They will also explore observations made initially in animal models of UCPPS to determine their relevance to humans. Finally, in Phase II the Network is expanding its collaborative efforts to include scientists outside of the Network itself—including other NIDDK-supported research networks—thereby increasing the number of and speed with which critical scientific questions can be pursued, to the ultimate benefit of persons living with or at risk of developing UCPPS.

More information can be found at the MAPP Research Network website:
www.mappnetwork.org

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