Collaborating with CTSAs to Advance Pain Research

April 15, 2011
NIH Natcher Auditorium

Meeting Summary – Final Document Prepared 06/22/2011

Overview

The NCRR/CTSA sponsored meeting entitled "Collaborating with CTSAs to Advance Pain Research" was held on April 15, 2011 at the Natcher Conference Center in Bethesda, MD. Attendance at the meeting included 80 participants, representing extramural investigators, Clinical and Translational Science Awards (CTSA) Institutions and NIH staff. The majority of participants at the meeting and all members of the meeting planning committee are members of the CTSA Pain Researchers Interest Group (CPRIG). CPRIG was initiated in July 2010 as an NCRR and CTSA supported effort to demonstrate how the CTSA Consortium can support needs and challenges of pain research.

Outcomes of the meeting included recommendations for future activities of CPRIG focused on: 1) Research collaboration across chronic pain areas; 2) Standardization of pain research instruments, tools and ontologies; 3) Promotion of successful research strategies introduced by other funded programs, such as the pre-existing NIDDK supported Multidisciplinary Approach to Chronic Pelvic Pain (MAPP; http://www.mappnetwork.org/) Network, the NIDCR supported Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA; https://www.oppera.org/) program and the FDA supported Analgesic Clinical Trials Innovation, Opportunities, and Networks Initiative (ACTION; http://www.actionppp.org/); and 4) working with CTSA Key Function Committees to support pain research.

Welcome and Announcements

Dr. Barbara Alving, NCRR Director, and Dr. Dan Rosenblum, NCRR, welcomed participants to the meeting. They acknowledged the diversity and heterogeneity of the group's membership and encouraged collaboration among them, emphasizing both the "power of one" and the "power of multiple." Dr. Alving also acknowledged members of the planning committee for their creative input into this meeting.

Meeting objectives were to:

- Identify needs, challenges, approaches and best practices related to pelvic and sickle cell pain
- Develop recommendations as to how the CTSAs can support pain research
- Provide a balance of scientific, practical and interactive sessions
- Plan future activities of the CTSA Pain Researchers Interest Group (CPRIG)
- Stimulate collaborations across academic institutions

Perplexing Pains Within: Pelvic and Sickle Cell Pain

G.F. Gebhart, Ph.D., University of Pittsburgh

Dr. Gebhart is currently Professor and Director of the Center for Pain Research at the University of Pittsburgh School of Medicine. Dr. Gebhart has published many original research papers and book chapters and has trained more than 30 Ph.D. students.

Dr. Gebhart provided an overview of "chronic pain within" syndromes, which include all functional gastro-intestinal (GI) disorders and possibly sickle cell disease pain. Dr. Gebhart discussed the high prevalence of comorbid conditions associated with functional GI disorders, including interstitial cystitis/painful bladder syndrome, vulvodynia, depression, anxiety and fibromyalgia. He discussed the current management of functional visceral disorders, which is characterized as "poor" due to an absence of knowledge about mechanisms that cause pain and hyperalgesia. He called on the audience to consider the current state of knowledge and to identify obstacles that currently limit understanding and management of pelvic and sickle cell pain.
Dr. Gebhart identified the following challenges that have impeded visceral afferent and nociceptor studies of "chronic pain within" syndromes. Dr. Gebhart recognized that this list does not include challenges to studying the central nervous system which are discussed in the reports from workgroups below and are generally agreed to be the predominant mechanisms for continuation of chronic pain and other pain-related symptoms. Overcoming these challenges, would allow immediate translation of results to clinical application:

- Internal organs are innervated by two different types of nerves that have some overlapping, but also distinct functions.
- Visceral sensory somata (i.e., dorsal root ganglion neurons) are often larger in size than what many investigators consider nociceptors and have often been excluded from the "small diameter" proportion of neurons considered as nociceptors.
- Most non-whole cell electrophysiology studies of the visceral innervation focus on mechanical stimuli (not unreasonably), but either do not appreciate or ignore that the mechanical stimulus which is pain-producing in hollow organs is stretch/distension.
- Potential interaction of visceral afferents with or modulation by the endogenous nervous system of an organ is essentially unknown and uninvestigated.
    - In general, the fine endings of visceral afferents in organ layers have not been successfully "visualized." The anatomical apposition/relation between the afferent and endogenous innervations is unknown.
- Potential neurogenic inflammatory contributions to visceral hypersensitivity are not widely considered as contributing to organ hypersensitivity or cross-organ sensitization suggesting that visceral afferents also have an efferent role in organ hypersensitivity. Functional characterization of visceral afferents via genomic and proteomic studies are likely to reveal them as 'biomarkers' and this knowledge significantly expand opportunities to study selected subsets of viscera afferents most relevant to visceral pain disorders.
- Visceral nociception does not have the characteristics of other nociceptors involved in chronic pain. Transient receptor potential (TRP) channels in cutaneous afferents are associated with temperature and chemical sensing, but not generally mechano-sensing whereas visceral TRPs V1, V4 and A1 [as well as acid sensing ion channels (ASICs) 2 and 3] do appear to play roles in mechanosensation.

The Pain Within: Sickle Cell Disease
Carlton Dampier, M.D., Emory University School of Medicine

Dr. Dampier is Professor of Pediatrics, Assistant Dean for Clinical Research, and Medical Director of the Office of Clinical Research at the Emory University School of Medicine.

Dr. Dampier's presentation focused on the pain prevalence and healthcare utilization of individuals with sickle cell disease. He reminded the audience that sickle cell disease pain starts at infancy and that it may be viewed as a chronic pain disorder, rather than a hemoglobinopathy associated with painful vaso-occlusive episodes. For many, but not all, individuals with sickle cell disease, chronic pain and acute exacerbations are not necessarily correlated with new or more severe injuries. Important lessons can be drawn between SCD pain and other pain disorders, and this meeting represents an opportunity to understand those similarities through detailed discussions.

Dr. Dampier highlighted the following challenges that have impeded studies of SCD pain:

- Because SCD pain begins in infancy and increases with age, childhood management is typically done in the home and through emergency room visits.
- Much of SCD pain data comes from hospital in-patient records for both children and adults, typically in response to crisis episodes.
- SCD pain has been managed as acute pain rather than chronic which has resulted in:
    - Treatment with opioids leading to significant addiction problems,
    - Difficulty studying the chronicity and transition from the acute to chronic state,
    - No therapeutic development for the chronic pain of SCD,
    - No understanding of the underlying pathology leading to SCD pain.

Overview of CTSA Program: Providing Investigators with Research Resources and Collaborative Opportunities
Anantha Shekhar, M.D., Ph.D., Indiana University; Dan Rosenblum, M.D., NCRR

Dr. Shekhar is the director of the Indiana Clinical and Translational Science Institute (CTSI) and Dr. Rosenblum is a medical officer in the Division of Clinical Research Resources at NCRR. They provided an overview of the CTSA program and talked about ways to leverage the CTSA network to enhance pain research. For instance, the CTSA Consortium represents an opportunity to access diverse skill sets and expertise across academic institutions. CTSA sites have formed regional consortia that can be tapped and leveraged. The Consortium has also produced a number of different resources that include educational materials for scholars and trainees, public-private partnerships, and the REDCap, a secure web application designed exclusively to support data capture for research studies. Drs. Shekhar and Rosenblum encouraged pain researchers to use these resources to aid and advance their research. More information on research resources and collaborative opportunities can be found at www.ctsaweb.org.

The MAPP: Straw Man for a Multidisciplinary Pain Network
Dan Clauw, M.D., University of Michigan

Dr. Daniel Clauw is a Professor of Anesthesiology, Medicine (rheumatology) and Psychiatry at the University of Michigan. He also serves as director of the Chronic Pain and Fatigue Research Center. Dr. Clauw provided background information regarding the pre-existing NIDDK supported Multidisciplinary Approach to Chronic Pelvic Pain (MAPP) Network (http://rt5.cceb.upenn.edu/mapp_web/MAPP_Home.html) . The MAPP Network is comprised of groups of pain researchers at 9 academic institutions that are focused on a broader "discovery" approach to the study of interstitial bladder pain syndrome and chronic prostatitis across epidemiology, phenotyping, neuorimaging, neurobiology, biomarker identification of organ to pain pathways.

Investigations include:

- The relationship between chronic pelvic pain syndromes and other chronic pain disorders

- Innovative epidemiologic studies
- Search for clinically important biomarkers
- Investigation of bacterial, viral and other infectious causative/exacerbating agents
- Novel brain imaging studies
- Animal studies to better understand the pathophysiology of these syndromes

MAPP discovery and collaborating sites span all regions of the United States and also includes one site in Kingston, Ontario. These sites make up a network that has successfully launched a variety of integrated studies using state-of-the-art technology and drawing from a pool of ethnically and geographically diverse research participants. This model is one that can be replicated by other sites and networks and additional studies may be incorporated into the existing MAPP network. A collaborative research study allows investigators and researchers to gauge information that may be lost by doing separate studies that have been designed differently.

Workgroup I: Clinical Features and Classification
Workgroup Leads: Dan Clauw,U. Michigan, Wendy Smith, NIDDK-NCC, Dan Rosenblum, NCRR

Workgroup I concluded that it would be beneficial to develop and obtain better tools to assess: 1) peripheral afferent drive versus central sensitization; 2) pain severity and its causes for specific pain conditions; and 3) those pain presentations that are common to all pain disorders and those that are unique. Additionally, these assessments should be done across multiple domains that include tissue damage, different levels of sensitization and pain experience.

CTSAs can support this area by:

1. Providing access to MAPP questionnaires, REDCap and PROMIS
    a. Research Electronic Data Capture (REDCap; http://project-redcap.org/) is a data management system developed and supported by the Vanderbilt University CTSA
    b. Patient Reported outcomes measurement Information System (PROMIS; http://www.nihpromis.org/about/centers) is an NIH supported standardized measurement system for patient-reported health status
2. Working with the CTSA Consortium Child Health Oversight Committee (CC-CHOC), NICHD, NIDDK, NHLBI, NINDS and other NIH ICs to:
    a. Identify patients at risk
    b. Reach out to pregnant and post-partum women
    c. Engage minorities, children of opioid addicts and neonates from NICU
    d. Encourage collaborative, prospective studies across health disciplines that can yield translational benefits

Workgroups II, III, and IV: CNS-Centricity; Afferent Drive; Cross-Organ Influences
Workgroup Leads: Emeran Mayer, UCLA, Rob Gereau, Washington U., Ray Dionne, NINR, Roger Fillingim, U.Florida, Anantha Shekar, U.Indiana, Jerry Gebhart, U.Pittsburgh, Nick Verne, OSU, Anna Malykhina, U.Pennsylvania, Kathy Hassell, U. Colorado, Kathleen Brady, MUSC

These workgroup sessions were consolidated due to joint opportunities and themes presented across the workgroups.

This consolidated group identified possible study areas for both abdominal/pelvic pain and SCD pain. For abdominal/pelvic pain, environment is highly relevant, particularly with regard to microbiota diversity and pathology. These insights further emphasize the need to focus on the relative importance of afferent drive in maintaining pelvic pain and to understand the relevance of chronicity in afferent input through the cycling in non-inflammatory visceral afferent stimulation, inflammation, tissue damage or other priming factors. In the discussion, there was a realization that the field would benefit from focusing on non-inflammatory mechanisms by which visceral afferent input to the CNS is enhanced. As the majority of chronic clinical pain syndromes (inflammatory bowel disease, interstitial cystitis, vulvodynia, non-cardiac chest pain) have no evidence for tissue inflammation, there is less rationale for focusing on inflammation and tissue damage in pain research. Thus, there is a need to focus on understanding the central mechanisms involved in chronic pain and the transition from acute to chronic pain.

With respect to SCD pain, study areas identified include SCD pain phenotyping through longitudinal studies, crisis pain versus ambient pain, and the better use of effective therapies for SCD pain such as hydroxylurea. Other opportunities include the studies of the relationship between pain priming and pain memory, particularly with respect to whether the initiating insult is environmental and/or requires tissue damage.

CTSAs can support these efforts by:

1. Promoting the standardization of processes and analyses
2. Emphasizing pain as a priority for mentors, scholars, and trainees
3. Facilitating cross-institutional collaboration:
    a. With standardized research techniques and data management
    b. Recruitment of patients, particularly for rare phenotypes

Workgroups V, VI and IX: Phenotyping; Genotyping; Biomedical Informatics and Imaging
Workgroup Leads: Roger Fillingim, U.Florida, Bill Maixner, UNC, James Taylor, NHLBI, Kameha Kidd, NCRR Maria Varela Diaz, Northwestern U., Carl Kesselman, USC, Karl Helmer, Harvard, Jody Sachs, NCRR, Emeran Mayer, UCLA, Carlton Dampier, Emory U., Dante Chialvo, UCLA, Kathleen Brady, MUSC

Three workgroups were collapsed into this session. The phenotyping focus was on pain profiles and demographic variables such as age, gender and race that should be accounted for across shared pathways of vulnerability. Importantly, there is a need for quantitative and qualitative clarification of clinical signs and symptoms. Additionally, comorbidities should be clearly documented and related to clinical presentation. There was general agreement that there is a need for assessing domains around peripheral versus central pain and pain sensitization versus amplification. Another risk domain that should be assessed is the psychosocial domain. The group also concluded that there are ways to better manage, coordinate and access data, and that data coordinating centers must be able to integrate across several different platforms and biological data. The goal of a data core would be to find commonalities and constructs across very diverse groups and information.

With respect to abdominal/pelvic pain, endophenotyping can best be accomplished with high throughput screening combined with: 1) structural and functional MR-imaging; 2) quantitative sensory testing across a variety of modalities including sensory summation, startle reflex to address pain inhibition and facilitation, response to tissue irritants such as capsaicin or menthol, ischemia such as that resulting from fatty acid oxidation, and measures of the autonomic nervous system; 3) psychological assessment using MAPP, OPPERA and other instruments; and 4) identification of environmental exposure.

The genotyping focus was on establishing genetic and molecular profiles through candidate genes, genome-wide association studies (GWAS), genetic sequencing and epigenetics. The critical issues surround IRB informed consent and study design.

- It will be essential for clinical and genetic investigators to work together to identify the optimal study design (heritability studies, family based studies, association studies, etc.).
- Developing proper informed consent documents that anticipate continued rapid changes in technology is important to allow for data sharing through the NIH supported database of genotypes and phenotypes (dbGAP) and for generation of induced pluripotent stem cells (iPS cells), should this be identified as a promising avenue of research on chronic pain.
- Genetic associations with pain phenotypes from GWAS will also be critical to focus analyses of exome or whole genome sequence data on a particular genomic region due to the sheer volume to variants encountered within a single individual (20,000 SNPs per exome and 1-2 x 10^6 SNPs per genome).
- Consideration should also be given to using gene expression studies for gene discovery in pain research. Use of study designs to identify expression quantitative trait loci (eQTLs) may be particularly useful with large cohorts pooled across institutions.

With regard to BioInformatics and Imaging, there was general consensus that there is a need for large scale multimodal data collection and analysis via: 1) a data coordinating center that includes a data repository with biological sample management integrated with other data, markers etc. via REDCap, PROMIS and/or electronic medical records; 2) a biostatistics/modeling approach with expertise in factor/cluster analysis, machine learning, forecasting and predictive modeling that accounts for natural history and predictive models for clinical pain profiles; 3) pathway analysis; and 4) ontologies.

CTSAs and the CPRIG can help in these areas by:

1. Developing and promoting uniform IRBs
2. Establishing pain phenotyping and biologic collection facilities
3. Sharing repository samples, such as the transMAPP Neuroimaging repository at UCLA that is a data repository for brain images collected by members of the MAPP Network to aid in developing biomarkers for chronic pelvic pain syndromes.
4. Tracking and managing biological sample uses
5. Forming an informatics team that can help:
    a. integrate and utilize the data sets
    b. develop policies for integration, data sharing and intellectual property across institutions
6. Developing ontologies related to complex pain conditions
7. Developing measures that are unique to the field
8. Developing a manual of procedures with recommendations for standardization across instruments and techniques

Workgroups VII and VIII: Biometrics and Biomarkers; Therapeutic Developments

Workgroup Leads: Anna Malykhina, U.Pennsylvania, Kathy Hassell, U.Colorado, Anantha Shekar, U.Indiana, Dan Clauw, U.Michigan, Ray Dionne, NINR, and Dan Rosenblum, NCRR

This session focused on biomarkers and biometrics. Biomarkers might predict subjects who are likely to respond, e.g. hypersensitivity. It would be beneficial to have biomarkers that are predictors of peripheral and central pain syndrome. In the absence of good diagnostic biomarkers, a therapeutic biomarker should be a surrogate for outcomes. Structural brain imaging data has been used in several large multicenter studies, including MAPP to generate a central repository of brain biomarkers, which can be correlated with other phenotypic metadata.

Newer techniques, such as resting state studies of the brain have the potential to become additional, standardizable biomarkers. Additionally, the group acknowledged that animal models are not yet ideal but good collaborative efforts are underway. The group concluded that animal models relevant to specific pain syndromes are needed.

The group also discussed the FDA's Analgesic Clinical Trials Innovation, Opportunities, and Networks (ACTION) Initiative which presents an opportunity to work collaboratively on standardization across clinical trials and development of new analgesic drug products for the benefit of the public health. However, there is a concern that populations may be segmented based on risk and response. That said, there are opportunities available through this mechanism that have the potential for advancing pain research provided the risks are addressed.

Conclusion and Next Steps

Drs. Gebhart and Rosenblum thanked everyone for their participation, reviewed outcomes from the meeting and highlighted next steps. An important general outcome was the agreement that the MAPP model including the transMAPP neuroimaging tool can be used as a model for bringing multiple institutions together around a pain area. This is particularly relevant to sickle cell pain, although assessments that are focused on adults would need to be re-calibrated to address the particular needs of children. Dr. Dampier developed a concept sheet which outlines how this relationship could work (see Appendix below).

#	Next Steps:	Leadership
1	CPRIG will convene meetings and workgroups to address the following issues: • Identify collaborative, prospective studies across health disciplines that can yield translational benefits • Develop specific recommendations to the CTSA Consortium for facilitating cross-institutional pain research collaborations around standardized research techniques, data management and subject recruitment • Develop guidelines for recruitment/retention for pain studies • *Optimize and standardize study design elements, specifically, adaptive trial design and develop opportunities to work with the FDA on the ACTION Initiative • Develop ontologies related to complex pain conditions • Identify and standardize measures that are unique to the field • Produce a manual of standardized procedures across instruments and techniques • Promote the standardization of processes and analyses • Develop collaborative cross-institutional studies to focus on the transition from acute to chronic pain • Develop collaborative cross-institutional studies around chronicity and comorbidity of pain	A.Sawczuk R. Gereau L.Porter
2	Establish partnerships and collaborations with CTSA Key Function Committees (KFCs) through working with them on ongoing projects around the following areas:	A. Sawczuk CPRIG workgroup members

	• *Community Engagement KFC & CC-CHOC* to identify and engage at-risk patients, minorities, pregnant and post partum females, children of opioid addicts and neonates from NICUs
	• **Clinical Research Management KFC & Regulatory Knowledge KFC* to develop and promote uniform/standardized IRBs
	• *Translation (T1) KFC* to establish pain genotyping, phenotyping and biologic collection facilities to:
	  o share repository samples
	  o track and manage biological samples
	• *Biostatistics (BERD), Informatics & Public Private Partnership KFCs* to develop policies across CTSA institutions for:
	  o Standardization and integration of pain instruments, research techniques and practices
	  o Data management and sharing
	  o Intellectual property practices
	  o Access and sharing of eHRs
	  o Developing a biostatistics modeling approach using factor/cluster analysis, machine learning, forecasting and predictive modeling to account for natural history of chronic pain profiles
	• *Education and Career Development KFC* to emphasize pain as a priority for mentors, scholars, and trainees
	• *Clinical Services Core KFC* to facilitate cross-institutional collaboration to recruit patients, particularly for rare phenotypes
	• Comparative Effectiveness Research (CER) KFC to identify opportunities for CER on pain symptom relief
	• *Clinical Research Ethics KFC* to develop standardized informed consent materials for data sharing of genetic and phenotypic data
		NCRR-CTSA Coordinators

3	**Identify opportunities for CPRIG & NIH IC Staff to discuss Sickle Cell Disease pain syndromes with regard to transition from acute to chronic pain, central pain, opioid-related syndromes, plus cultural and psycho-social issues through tools provided by MAPP, OPERA and the CTSA Consortium	Workgroup leads NIH IC staff

4	Communicate meeting outcomes:
	• **Post information from the April meeting on the CPRIG Wiki and the CTSA public website (www.ctsaweb.org):
	• **Prepare report and share with:
	  o NCRR leadership
	  o CTSA Consortium Steering Committee
	  o NIH Pain Consortium
	  o CTSA Pain Researchers Interest Group (CPRIG)
		A. Sawczuk
		H. Aden
		
		A. Sawczuk

*** Project recently started**
****Project in progress**

*****Project completed**

Links to Meeting Presentations:
https://www.ctsawiki.org/wiki/x/goFGAg
http://www.ctsaweb.org/

Planning Committee: Kathleen Brady, MUSC; Dan Clauw, U.Michigan; Doris Cope, U.Pittsburgh; Carlton Dampier, Emory U.; Gerald Gebhart, U.Pittsburgh; Robert Gereau, Washington U.; Curtis Lowery, U.Arkansas, Harvey Luksenburg, NHLBI; Linda Porter, NINDS; Andrea Sawczuk, NCRR; Anantha Shekhar, U.Indiana; Wendy Smith, NIH/OD; Michael Vasko, U.Indiana.

Appendix to April 15th Pain Meeting Report:

Concept Sheet: Multidisciplinary Approach to Study of Chronic Pediatric and Adult Pain in SCD (MAPP-SCD)

Prepared by Carlton Dampier MD 5/25/11

Goal:
Leverage MAPP Network expertise and infrastructure to develop a multidisciplinary lifespan network to study transition of acute to chronic pain in sickle cell disease. This additional MAPP network would have similar key focus areas as the existing MAPP Network including
■Epidemiology of acute and chronic pain in SCD over the lifespan
■Phenotyping of sickle pain-related symptoms
■Neuroimaging / Neurobiology Studies of sickle pain
■Identification of Biomarkers of Disease and/or pain symptoms
■Characterizations of Organ Cross-Talk / Pain Pathways (?)

Organization:

1. **Ten to 12 discovery/recruitment recruitment sites that would be able to recruit adult and/or pediatric SCD subjects, and/or pediatric or young adult pain subjects (IBD, fibromyalgia, rheumatologic, disorders), and/or age and ethnically matched controls. These will be CTSA sites (likely sites include Emory, U Penn, U Wash, U Cincinnati, Children's National Medical Center, Medical College of Wisconsin, Boston University, Johns Hopkins, U Illinois-Chicago, Northwestern U, U Pittsburg, U Alabama)**
2. **Utilize MAPP network core sites for infrastructure including Tissue Analysis and Technology Core; Data Coordinating Center; Neuroimaging**

Expertise:

1. **All sites will have expertise in care of either pediatric or adult (or both) individuals with SCD, and also should be able to recruit normal controls. Most sites will have the capability to recruit pediatric and young adult subjects with chronic pain. All sites should have the capability to obtain biomarker studies.**
2. **Several sites will have the expertise to conduct QST on pediatric and or adult participants.**

3. **Many sites will have capability to perform MRI and/or fMRI studies in pediatric and/or adult participants**
4. **Several sites may have capability to perform biomarker or genetic analyses specific to SCD.**

SCD Cohorts:
Young Adolescent: Age 12-16; Older Adolescent: Age 17-21; Young Adult: Age 22-26; Adults: Age 27-31
(Will need more discussion but 100 in each cohort seems like a feasible goal, but little information on incidence or prevalence of chronic pain exists in the SCD population to guide more detail sample size estimates; will also need some discussion of size of positive and negative control samples)
Next Steps:

1. **Access to MAPP Portal to look at protocols and assessments in more detail**
2. **Workshop or other meeting forum of adult and pediatric pain experts and some SCD experts**
    a. **To discuss applicability of current MAPP assessments to a pediatric (adolescent) and young adult population; and to an SCD population**
    b. **To discuss what additional assessments may need to be added that are unique to pediatrics, such as developmental, family, etc issues**