17th Annual NIH Pain Consortium Symposium on Advances in Pain Research

Pain Management Through the Lens of Whole Person Heath

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ZoomGov

Junior Investigator Poster Abstracts

(Listed in order of presentation)

Session 1: June 1, 2:15pm

The Impact of Chronic Pain Condition on Mental Health Outcomes During the COVID-19 Pandemic

Titilola Akintola, Maya Delity, Nicole Antkiewicz, Joyce Chung, Lauren Atlas

The COVID-19 pandemic has extensive health implications for everyone, with a disproportionate effect in chronic pain (CP) populations[6]. The effects of stressors may also be heightened for CP patients, many of whom have experienced reduced access to pain management[3]. The contrasting evidence from previous reports of CP patients during the pandemic suggest that health outcomes may differ based on pain condition[1 4, 5]. However, to our knowledge, no studies have compared outcomes across different pain conditions.

To address this gap, we investigated the impact of CP condition on mental health outcomes during the pandemic. We hypothesized that varying CP conditions will impact measures of distress and loneliness, anxiety and depression differentially. 3,655 participants provided baseline and biweekly self-report measures of physical and mental health outcomes from April 2020-May 2021. We collected measures of distress (Kessler-5 Distress Scale), loneliness (UCLA-loneliness scale), anxiety and depression (using the DSM 5 X-C). At the end of the study, 2,398 participants completed a Chronic Pain Graded Scale (CPGS). To address the impact of different pain conditions on psychological outcomes, these analyses focused on the 508 participants endorsing only one pain condition, lasting longer than 6 months. Pain classification was done using the International Classification of Disease 11th edition (ICD-11)[8]. We ran ANOVAs and Tukey's post-hoc analyses to determine the effect of pain condition on the 4 psychological measures. We included average pain intensity and mental health status as covariates.

Average pain intensity did not differ by pain condition (r= 0.017, p=0.71). Across pain categories, individuals with higher average pain intensity reported greater average distress (r=0.32, p< .001), loneliness (r=0.22, p<.001), anxiety (r=0.31, p<.001) and depression (r=0.28, p<.001) across the six-month period. There was a significant main effect of pain condition on mean distress ($F_{1, 489}$ = 5.43, p< .001), loneliness ($F_{5, 489}$=6.49, p =0.04), anxiety ($F_{5, 489}$=4.922, p< .001) and depression ($F_{5, 489}$=5.83, p < .001). Post-hoc analyses revealed that participants with primary chronic pain reported greater average distress (M=9.15, SD=3.8) than those with neuropathic pain (M=6.14, SD=4.3, p= 0.02), visceral pain (M=6.30, SD=3.9, p< .001) and musculoskeletal pain (M=6.08, SD=3.8, p<.001). While patients with headache or orofacial pain reported more mean distress (M=7.73, SD=3.9) than those with musculoskeletal pain (M=6.08, p=0.01). Similar patterns were observed for mean depression and anxiety. Patients with primary chronic pain reported greater mean depression (M=4.19, SD=1.9) than those with musculoskeletal pain (M=2.93, SD=1.7, p<.001) and visceral pain (M=2.94, SD=1.8, p<.001) while those with headache or orofacial pain reported more average depression (M=3.62, SD =1.7) than those with musculoskeletal pain (M=2.93, SD=1.7, p =0.046). Likewise for anxiety, primary chronic pain patients reported greater mean anxiety (M=3.86, SD=1.8) than musculoskeletal pain (M=2.64, SD=1.8, p=0.001) and visceral pain patients (M=2.77, SD=1.9, p=0.012), while those with headache or orofacial pain reported more average anxiety (M=3.38, SD=2.1) than musculoskeletal pain patients (M=2.64, SD=1.8, p= 0.045). Although we observed a main effect of pain condition on loneliness, post-hoc comparisons did not reveal any significant differences between pain conditions. There were no interactions with intensity and pain condition for other mental health outcomes.

While it is known that CP patients experience greater psychological distress than people without CP[2], these findings provide an explanation for the contrasting health outcomes reported during the pandemic. Further studies will assess the impact of pain condition and multiple pain comorbidities on other health outcomes. We recognize that the reliance on retrospective memory of pain over the survey period may be a limitation. However, these results indicate that recommendations about

pain management may need to consider the unique needs of CP patients to ensure effective care during the ongoing pandemic.

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Acupuncture for Chemotherapy-induced Peripheral Neuropathy Pain

Ting Bao MD, DABMA, MS, Memorial Sloan Kettering Cancer Center

Chemotherapy-induced peripheral neuropathy (CIPN) is a painful, debilitating complication of neurotoxic chemotherapy that affects up to 68% of cancer patients. This condition may last from months to years, and is associated with significant pain, tingling, and numbness, as well as worsened function and quality of life. Despite growing research, management of CIPN remains a major clinical challenge. Additional non-pharmacological treatments are needed. Acupuncture is a widely used, minimally invasive, and safe traditional Chinese medicine technique currently available for patients in 75% of academic cancer centers in the United States. Even though acupuncture has been established as an effective treatment for reducing chronic musculoskeletal pain, its role in reducing neuropathic pain has been poorly characterized.

Dr. Ting Bao and colleagues at Memorial Sloan Kettering Cancer Center recently completed a pilot randomized controlled trial (RCT) among solid tumor patients with moderate to severe CIPN symptoms (n=75). Participants who received electro-acupuncture (EA) treatments over eight weeks experienced greater CIPN pain reduction at weeks 8 (end of treatment) and 12 (follow-up) when compared to sham acupuncture (SA) and usual care (UC) (week 8: -1.75 numeric rating scale (NRS) units in EA vs. -0.91 in SA vs. -0.19 in UC; week 12: -1.74 in EA vs. -0.35 in SA vs. -0.33 in UC) without any significant side effects. Further, the pilot study showed that compared to SA and UC, EA normalized tactile sensitivity measured by quantitative sensory testing (QST) more than SA or UC at week 8. They also found that EA produced greater pain reduction in patients with intact baseline conditioned pain modulation (CPM), a QST measure of the endogenous descending pain inhibitory pathway, compared to those with impaired baseline CPM (week 8: -1.57 in intact CPM vs. -0.6 in impaired CPM), suggesting that those with more efficient pain inhibitory mechanisms are more amenable to EA treatment effects. In addition, prior studies showed that patients with higher baseline pressure pain thresholds (PPT) were more likely to respond to real acupuncture than to sham acupuncture.

Based on these pilot data, Dr. Bao and her team are conducting a modified double-blind (patients and evaluators blind), randomized, placebo (SA)-controlled clinical trial to determine the efficacy of acupuncture in cancer survivors with moderate to severe CIPN pain (n=250). The objectives are to determine the efficacy of EA in reducing CIPN symptoms and identify neurobiological markers with QST that predict treatment response to EA.

Their **specific aims** are:
Aim 1: To determine the efficacy of an eight-week EA treatment on CIPN symptoms among cancer survivors with moderate to severe CIPN pain. Aim 2: To evaluate the effect of EA vs. SA on small sensory fiber function, as measured by QST. Aim 3: To evaluate whether baseline QST outcomes, including CPM and PPT, predict response to EA. So far, Dr. Bao and colleagues have enrolled 35 patients and collected patient-reported outcome and QST data from them. The team expects to complete accrual at the end of 2024. The results of the trial may help determine if QST can be used to predict the effectiveness of EA,

potentially leading to a new approach for personalized CIPN treatment. This trial has the potential to establish a new standard of care for CIPN that will significantly improve quality of life for millions of cancer survivors.

Novel Mechanistic Insights into Alcohol Analgesia

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Objective. To improve understanding of biopsychosocial mechanisms underlying alcohol analgesia and the negative reinforcing effects of alcohol use in the context of pain.

Background. Self-management of pain using alcohol results in increased risk for alcohol-related consequences and significant societal costs. A limited body of laboratory-based evidence indicates alcohol consistently produces increased pain threshold and decreased pain intensity in people without chronic pain. However, there are significant gaps in understanding regarding biopsychosocial mechanisms underlying this effect, as well as potentially critical moderators. Furthermore, advancement in understanding motivation to use alcohol in people with pain has also been hampered by an implicit assumption that the negative reinforcing effects of alcohol use for pain are fully reflected by quantitative changes in sensory function (e.g., pain thresholds). This is assumed despite evidence from the pain literature that perception of relief likely reflects a complex, multifactorial process. This project addressed these gaps in knowledge.

Specific Aims. Aim 1. Characterize moderators of alcohol analgesia in non-treatment seeking social drinkers, including sex, chronic pain status, and family history of alcohol problems. Aim 2. Identify psychosocial factors underlying individual differences in the reinforcing effects of alcohol use (i.e., perception of pain relief) and alcohol analgesia.

Results and Significance. Data from two studies of alcohol analgesia using acute oral alcohol challenge (Study 1 [R01AA025337], n=68; Study 2 [R21AA026805], n=51) contributed to this analysis (total N=119; 53.8% women). Study 1 included only pain-free social drinkers, while Study 2 included pain-free social drinkers (n=30) and individuals with chronic jaw pain (n=21). Twenty-five individuals endorsed having at least one parent with a family history of alcohol problems (FH+). In both studies, participants completed two double-blind laboratory sessions involving consumption of either a placebo (0.00 g/dL target BrAC) or active (0.08 g/dL target BrAC) beverage, followed by quantitative sensory testing (Study 1: heat pain, Study 2: pressure algometry) to determine pain threshold, pain intensity, perceived pain relief resulting from beverage consumption, and subjective intoxication. Expectancy of alcohol analgesia (EAA) and pain-related anxiety were also assessed. Results of combined analyses indicated alcohol intake significantly elevated pain threshold, regardless of sex or FH status ($F_{1,115}$=13.25, p<.0001, η^2_p=.10). A similar effect was identified for ratings of perceived pain relief ($F_{1,115}$=52.58, p<.0001, η^2_p=.34). However, alcohol-related reductions in experimental pain intensity were significantly greater in women than men ($F_{1,115}$=5.30, p=.02, η^2_p=.04). No significant moderating effects of FH status on beverage condition was found, although FH+ men had lower pain thresholds ($F_{1,115}$=8.556, p=.004, η^2_p=.07) and reported greater pain intensity ($F_{1,115}$=5.88, p=.017, η^2_p=.049) than any other group. Contrary to expectations, results of Study 2 indicated that chronic pain status did not significantly moderate effects of alcohol intake on pain threshold, pain intensity, or perceived relief, although individuals with chronic pain had lower pain thresholds and greater pain intensity. Finally, hierarchical linear regression analysis identified EAA (β=.24, p=.003) and subjective intoxication (β=.55, p<.0001), but not pain intensity (β=*.13,* p=.11) nor pain threshold (β=*.05,* p=.53), as significant predictors of perceived relief in the active alcohol condition (total R^2=.41).

Conclusions*.* Our results extend prior literature indicating that alcohol has acute analgesic effects in laboratory settings by indicating that, despite group differences in pain sensitivity, these effects may not be contingent on FH or chronic pain status. They also provide novel evidence that the negative reinforcing effects of alcohol (as indexed by perceived pain relief) are powerful and more closely reflect EAA and subjective intoxication than measures of pain threshold or intensity.

Evaluating Potential Disparities by Sociocultural Factors in Pain Assessment

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Objective: To determine if perceivers exhibit disparities in an experimental model of pain assessment

Specific Aims: 1) Determine if our perceivers identify pain in a videoset we created of acute pain in a diverse human cohort 2) Determine if our perceivers replicate commonly observed disparities in clinical pain assessment and 3) Assess our individual difference measures as potential moderators and targets for intervention of pain assessment biases Background: In clinical contexts, historically marginalized populations (e.g., women and people of color) experience worse and more frequent pain and receive less pain treatment. Researchers have begun to investigate potential mechanisms underlying inequities in pain assessment (e.g., facial expression perception), but the results have been inconsistent. This may be due to limited resources to adequately assess potential biases, as no databases of diverse facial expressions of real pain exist. In response, we ran experimental models of acute pain and filmed participants to create a videoset of facial expressions of pain across a diverse cohort. We presented those videos in this experiment to better assess potential biases in pain assessment. We asked our perceivers to categorically rate if they perceived pain or not in each video and to rate intensity on a 0-100 Visual Analogue Scale. Finally, we had perceivers fill out several individual difference measures to assess for potential moderators of pain assessment bias.

Results and Significance: Using videos of real acute pain, we replicated disparities of pain assessment. We observed a greater likelihood in our perceivers to rate pain in categorical judgments of pain for videos depicting men ($b = -0.35$, $p = 0.04$) or White targets ($b = -0.82$, $p < 0.001$) compared to videos depicting women or Black targets. This bias interacted with several experimental factors (e.g., greater facial expression intensity in the video increased the odds a perceiver rated a trial as painful, but this effect was greater for videos with White targets, $b = -0.03$, $p = 0.009$) and interacted with individual difference measures of racial bias and perceived similarity. Individuals who endorsed greater levels of racial bias ($b = -0.33$, $p = 0.03$) and rated greater perceived similarity ($b = -2.56$, $p < 0.001$) to White compared to Black targets had greater odds of rating a trial as painful for White targets compared to Black targets. Beyond categorical pain ratings, we observed greater pain intensity attributed to White targets compared to Black targets in our sample ($b = 75.0$, $p = 0.03$) and this bias also interacted with several experimental factors and our individual difference measures of racial bias and perceived similarity. Our outcomes suggest that ecologically valid depictions of pain can lead to experimental replications of disparities in pain assessment. Furthermore, these disparities seem to increase based on multiple experimental factors, racial bias endorsement, and perceived similarity – suggesting several potential targets for pain assessment intervention.

Visualization of Trigeminal Ganglion Sensory Neuronal Signaling Regulated by Cdk5

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Cyclin-dependent kinase 5 (Cdk5) is a unique member of the serine/threonine kinase family. It is a key neuronal kinase involved in brain development, neurotransmitter release and pain signaling. However, the specific role of Cdk5 in orofacial pain signaling in mouse trigeminal ganglion (TG) primary neurons remains elusive. In this study, we used an optimized intravital imaging technique to monitor whole TG neuronal activity following different stimuli in the orofacial region of mice. Our aim was to elucidate the role of Cdk5 in regulating primary sensory neuronal activities in response to orofacial pain. Cdk5 activity is regulated by binding to its activator p35. To understand how various stimuli are represented in the TG, we bred GCaMP6; Trpv1-cre mice with p35-/- and p35 overexpression (Tgp35) mice to genetically decrease or increase the Cdk5 activities in these mice, respectively. We used an intravital imaging technique to directly measure mechano-, chemo-, and thermo-evoked responses in hundreds of neurons across the TG in these mice. Additionally, we tested whether the Cdk5 inhibitor peptide TFP5 can alleviate inflammatory pain in mice. Ca2+ transient data extracted from live imaging showed that mechano-, chemo-, and thermo- stimuli trigger various neuron firing dynamics. We found that total Ca2+ intensities are decreased in response to pain stimuli in p35-/- mice compared with controls, while Tgp35 mice showed the opposite responses. In mice with orofacial inflammation, application of TFP5 decreased both total Ca2+ intensities and the extent of polymodal signaling associated with inflammatory pain compared with control peptide-treated mice. We have explored directly the spatial and real-time characteristics of activity across the TG upon orofacial stimulation and have

observed clear differences between different stimuli. We demonstrated that Cdk5 can regulate primary sensory neuronal activities in response to pain, and that the Cdk5 peptide inhibitor is a promising non-opioid candidate for pain treatment.

Session 2: June 1, 4:25pm

Prehospital Opioids and Short-term Outcomes for Older Adults with Fall-Related Injury

Molly P Jarman, PhD, MPH; Ginger Jin, MS; Sarah Berry, MD; Elena Losina, PhD, MSc; Joel S. Weissman, PhD; Ali Salim, MD

Objective: The primary objective of this work is to improve our understanding of the use of opioid analgesic medication by emergency medical services (EMS) personnel to treat pain in older adults with traumatic injury.

Specific Aim: To determine if prehospital pain management interventions are associated with improved short-term health outcomes for older adults with fall-related injury.

Background: National guidelines for prehospital treatment of injured patients recommend treating moderate to severe pain with opioids, yet only 10% of injured older adults receive prehospital pain management, partly due to concerns that exposure to opioids can cause acute delirium and long term substance use disorder. Conversely, injured older adults with poorly managed acute pain are at higher risk of developing delirium. For this paper, we sought to determine the association between EMS administration of opioid analgesia in the prehospital setting and short-term health outcomes for older adults with fall-related injury.

Methods: Study participants included Illinois residents, age ≥65, enrolled in fee-for-service Medicare, and with an emergency department (ED) encounter or inpatient admission for a fall during 2014-2015. Medicare claims were linked with prehospital patient care reports from the Illinois Department of Public Health. Outcomes including inpatient length of stay (LOS), ICU LOS, and diagnosis of delirium (based on inpatient or ED diagnosis codes) were compared for patients with and without prehospital opioid analgesia using logistic (delirium) and Poisson (LOS) regression with inverse probability of opioid analgesia treatment weighting based on age, sex, race, frailty, Charlson comorbidity index, injury severity score (ISS), an indicator for traumatic brain injury, total prehospital time and vital signs, and trauma center level.

Results: We identified 28,150 older adults with fall-related injury and corresponding prehospital data, 70% were female, 94% white, mean age was 82, 28% had ISS ≥9, and 3% received prehospital opioid analgesia. Mean inpatient LOS was 4 days, mean ICU LOS was 3 days, and 2% were diagnosed with delirium. Prehospital opioid analgesia was associated with a 9% decrease in LOS (IRR = 0.91, 95% CI: 0.85, 0.98), and a 20% decrease in ICU LOS (IRR = 0.80, 95% CI: 0.65, 1.00). The association between prehospital opioid administration and delirium did not reach statistical significance (OR = 1.11, 95% CI: 0.36, 3.42).

Conclusions: Administration of opioids in the prehospital setting is associated with shorter inpatient and ICU length of stay for older adults with fall-related injury without substantially increasing risk of delirium. Additional research is needed to identify long-term harms or benefits of prehospital opioid analgesia for injury older adults, and to identify barriers to EMS administration of opioid analgesia in the prehospital setting.

Engaging A Limited English Proficient Population in Designing and Evaluating a Pain Quality Assessment Information Visualization Tool to Improve Patient-Interpreter-Provider Communication

Maichou Lor, PhD, RN, Nancy Yang, BSN(c), Uba Backonja, PhD, RN and Suzanne Bakken, PhD, RN, FAAN, FACMI

Objective: To develop a culturally appropriate information visualization (InfoViz) pain quality assessment tool for Hmong patients with limited English proficiency (LEP) using a multi-stepped, user-centered approach. We conducted this study with LEP Hmong, bilingual Hmong, and Hmong interpreters

Specific aim(s):

1) To evaluate and refine the pain quality infographics for inclusion in the tool through participatory design sessions
2) To organize the pain quality infographics on the tool to match the mental models of LEP Hmong through card sorting sessions
3) To identify which tool accurately represents LEP Hmong patients' mental models and is preferred for use in the clinical setting using qualitative interviews

Background: Pain diagnosis and management require effective communication between patients, interpreters, and health care providers. Research shows that patients often express pain information (i.e., pain quality) in metaphorical or culturally based terms that do not match the medical terms of the providers and knowledge of interpreters, resulting in suboptimal patient-provider communication. One patient group at high risk for pain communication misunderstandings and disparities in pain care is the Hmong. The Hmong in the United States are from an agrarian society and are refugees. Pain is understood and communicated through cultural metaphors that conflict with providers' pain language and Hmong-speaking interpreters struggled to interpret the metaphors. Consequently, Hmong patients, health care providers, and interpreters desire to have a pain assessment using InfoViz to facilitate pain communication. Information visualization tools offer a potential solution to such pain communication challenges.

Results: A total of 55 Hmong participants (27 LEP patients, 15 bilingual patients, and 13 interpreters) participated in the study. LEP Hmong participants designed an infographic corresponding to each pain metaphor commonly used by verbally describing their mental infographics of the pain metaphors to a Hmong-speaking illustrator. Ultimately, this work yielded an initial set of 54 images corresponding to each pain metaphor and was used for evaluation and refinement in this study. Participants provided four common themes for refinement of the pain quality infographics: (1) use of culturally-relevant colors, (2) having human anatomy with location-specific drawings, and (3) squiggle lines, action-specific. For each iteration of the design, the accuracy, comprehension, and cultural appropriateness of the pain pictogram improved over time. At the end of the participatory design sessions, 15 pain quality infographics were selected. There were three main themes of organization of mental models from the 15 infographics: sensation (n=15; 71.4%), localization (n=6; 28.6%), and severity (n=5; 24.3%) of pain quality. Most participants selected the localization of pain qualities as the most accurate tool representing their mental model and preferred using it in the clinical setting.

Significance: To our knowledge, this is the first study that developed and evaluated pain quality infographics with an LEP population and medical interpreters. Overall, the outcome of three stepped user-centered approaches led to the development of a culturally appropriate pain quality infographic assessment tool for LEP Hmong patients. The findings of this study will hopefully increase the chances of successful implementation in clinical settings to improve LEP patient, interpreter, and provider communication about pain.

Sociocultural Mechanisms Underlying Disparities Pain Assessment and Treatment During Telemedicine Decisions During Telemedicine

Elizabeth A. Reynolds Losin, Theoni Zoi Varoudaki, Maria Llabre

Objective: In the current study, our objective was test how clinicians' pain stereotypes about different ethnic and racial groups contribute to well-documented ethnic and racial disparities in acute pain assessment and treatment during telemedicine. We accomplished this objective through the following specific aims:

Specific Aims:

Aim 1: To test the effects of patient race and ethnicity on pain assessment and treatment decisions. We conducted a series of simulated telemedicine clinical interactions where medical trainees saw mock shoulder injury patients of different demographic groups through Zoom and made pain assessments and treatment recommendations.

Aim 2: To test whether clinician's ethnic and racial pain stereotypes mediate the effects of patient race and ethnicity on pain assessment and treatment decisions. Structural equation modeling was used to test potential mechanisms underlying patient demographic effects on pain assessment and treatment with the clinician – patient dyad being the unit of analysis.

Background: Unequal prescribing of opioid and non-opioid analgesics among racial and ethnic groups contributes to two major health disparities in the United States. Overprescribing of opioid analgesics to treat both acute and chronic nonmalignant pain, especially in non-Hispanic whites, has fueled an epidemic of opioid abuse. Under prescribing of opioid and non-opioid analgesics to minoritized individuals and women, even when their use is medically indicated (e.g., acute and cancer pain), reduces the effectiveness of pain management in these groups. One possible mechanism underlying analgesic prescribing disparities is that clinicians make pain assessments and treatment decisions based on inaccurate demographic pain sensitivity and opioid abuse stereotypes. The rise in telehealth due to the COVID-19 pandemic may exacerbate these disparities due to the decrease in patient-specific information available to the clinician (e.g., lack of a physical clinical exam, reduced visual information about the patient's condition).

Results: We found that clinicians' demographic pain sensitivity stereotypes, but not patients' reported pain ratings, predicted clinicians' pain assessment and treatment decisions suggesting that patients' ratings of their own pain are discounted over the clinicians' own beliefs about the patient. The more sensitive clinicians believed people from a patient's

racial group were, the more intense the clinicians assessed the pain of that patient. In addition, more advanced medical experience was associated with higher assessed patient pain intensity via a positively related mediator: Higher belief that typical individuals from the patients' racial groups were more sensitive to pain. In turn, this higher belief in more pain sensitivity of a group predicted higher likelihood of prescribing opioid analgesics for that group via higher assessed patient pain intensity. Furthermore, only assessment of pain intensity and not assessment of pain unpleasantness predicted the prescription of oral opioid analgesics by the clinicians, and more positive attitudes towards opioids also predicted higher prescriptions of opioid analgesics to patients as well.

Significance: Our findings suggest that clinicians may rely more heavily on their stereotypes about the typical pain sensitivity of people from a patients' ethnic group, e.g., that Black Americans are less sensitive to pain than non-Hispanic White Americans, than the patients' own description of their pain. These findings further suggest that interventions aimed at reducing clinicians' pain sensitivity stereotypes and increasing their use of patient-provided information could help mitigate demographic pain treatment disparities.

The Potential Role of Neurobiological Mechanisms of Stress in Pain Maintenance and Mind-Body Intervention Response in Youth with Chronic Pain

Sarah Nelson, PhD, David Borsook, MD/PhD, & Michelle Bosquet Enlow, PhD

Background: Pediatric chronic pain (i.e., pain lasting > 3 months) is a serious public health problem resulting in significant healthcare utilization and disability. Youth with chronic pain frequently report exposure to adverse childhood experiences (ACEs; abuse/neglect, etc.), and a significant subset experience pain-related and psychosocial impairment long-term, including into adulthood. Preliminary research indicates that allostatic load (AL), or "wear and tear" on multiple physiological regulatory systems (e.g., nervous system, cardiovascular, metabolic) due to stress, may exacerbate pain intensity and chronicity. Similarly, evidence suggests that the hippocampus, a brain structure that is among the most deleteriously affected by stress, plays a role in pain perception. Because youth with chronic pain are highly stressed, interventions that address these maladaptive stress responses, such as mindfulness-based stress reduction (MBSR), may be particularly relevant by modulating stress-induced alterations of the hypothalamic-pituitary-adrenal axis, autonomic nervous system, and brain structure (e.g., hippocampus) and by promoting resilience to a reoccurrence of impairment. However, the efficacy of these interventions in youth with chronic pain in a mechanistically informed context has not been examined, despite the larger research effort to move towards mechanistically informed treatments in the pain field.

Objectives: Objectives of the current presentation are to (a) summarize my research to date on neurobiological mechanisms connected to the physiological stress response in youth with chronic pain and (b) highlight my ongoing research funded by the NCCIH that examines these mechanisms in relation to the effectiveness of mind-body interventions in pediatric chronic widespread pain. These populations have been historically difficult to treat with traditional non-pharmacological therapies; consequently, mechanistic research on intervention response in these youth is a critical area of need.

Specific Aims: Specific aims include 1) outlining my preliminary investigation into the measurement and incidence of AL risk in youth with chronic pain, 2) delineating brain regions of interest impacted by stress that may be important in mind-body intervention response and pain maintenance, and 3) providing an overview of my ongoing research that further investigates the proposed relations between neurobiological mechanisms of stress and mind-body intervention response in youth with chronic pain.

Results: Preliminary results from my pilot investigations suggest that more than 50% of youth with chronic pain are at high risk for AL (positive for two or more risk factors). Further, AL may moderate the association between psychosocial and functional outcomes in youth with chronic pain, which highlights the potential role of stress "wear and tear" in modulating pain-related functioning. Building on these findings, we are currently carrying out an NCCIH-funded clinical trial that aims to further elucidate the role of AL in pain-related functioning and provide new evidence on the potential role of AL and brain-based maladaptation to stress in mind-body intervention response. As part of this study, participants complete a baseline visit with fMRI and quantitative sensory testing, a multifactorial AL composite (e.g., salivary glucocorticoids [cortisol, DHEA], BMI, waist-hip ratio, blood pressure), self-report of intervention engagement, and questionnaires on stress and ACEs exposure. We then repeat collection of the AL composite measure, intervention engagement, and questionnaires at 4-month follow-up.

Significance: Evidence of elevated AL risk factors and functional connectivity changes in youth with chronic pain would offer strong support for the importance of targeting the physiological stress-response using a mind-body approach to reduce

long-term disability. Critically, objective physiological evidence of the role of stress in pain will also provide critical support for larger trials of tailored and mechanistically informed treatments with the overarching goal of optimizing care for these vulnerable youth.

Step by Step Towards Improved Health: Sensory Phenotyping of Feet Affected by Morton's Neuroma and Reducing Refractory Pain With an Injection of Resiniferatoxin (RTX)

Ellen Staedtler, MD, PhD., Department of Perioperative Medicine, Clinical Center, NIH

Peripheral neuropathic pain occurs following a variety of physical, disease-related, or chemotherapy-induced nerve damage. It is a major chronic pain problem affecting 7-10% of the general population and is notoriously difficult to treat. Here we explore a novel interventional, highly selective axonal inactivation therapy to treat pain from Morton's neuroma (MN), a well-delineated neuropathic pain disorder. MN is a degenerative peripheral nerve lesion located in the forefoot that is a source of chronic pain and substantially affects physical activity.

While in the early stage of the disease conservative measures like physical therapy or metatarsal padding can be effective, approximately 50% of patients seek additional relief with injections of corticoids, often in combination with a local anesthetic, and sclerosing alcohol injections. These procedures cannot be repeated endlessly due to accumulating side effects or are non-selective in nature. In about one third of cases pain is not effectively reduced, so patients chose to have surgery, mostly neurectomy, which also is not completely effective in all cases.

Because of these limitations we are developing an alternative treatment consisting of a local, perineural injection of resiniferatoxin (RTX). RTX causes a long-lasting chemoaxotomy of the RTX-susceptible nociceptive fibers and does not affect other sensory modalities, motor fibers or surrounding tissue.

RTX is a potent analog of capsaicin the active ingredient in hot pepper. RTX is extracted from the latex of succulent plants notably Euphorbia resinifera from the Atlas mountains in Morocco. The dried latex was used as a remedy against muscle and tooth aches more than 2000 years ago. The discovery of its molecular target, TRPV1, approximately 20 years ago led to renewed interest in the substance as a selective and long-lasting remedy for localized pain conditions. TRPV1 is an ion channel activated by heat, inflammation, and RTX and is found in nociceptive neurons of the PNS. Thus, RTX does not act in the CNS and is a non-opioid analgesic. The Department of Perioperative Medicine was involved in discovering the cellular effects of RTX, its analgesic actions in several animal models and presently is conducting clinical trials in patients with advanced cancer pain.

MN is an ideal model to study chronic nerve-injury induced neuropathic pain, its treatment, and its resolution particularly for evaluating the effects of localized application of RTX. The symptoms include spontaneous and burning pain, mechanical allodynia, and thermal hyperesthesia. Although Morton's neuroma is a common pain condition, little experimental data is available about sensitivities to different test stimuli in the neuropathic area. We will conduct a detailed characterization of the symptom profiles of MN patients by using a validated Quantitative Sensory Testing (QST) protocol in collaboration with the NIH Pain Research Center. QST provides reliable and validated safety and efficacy outcome measures for the clinical trial. We have initiated a pilot study to evaluate how to test the affected foot in controls and MN patients. We have started recruiting and measuring healthy volunteers who will serve as a matched control population.

The protocol for the clinical trial (Phase I Clinical Trial using resiniferatoxin (RTX) for the management of refractory Morton's neuroma pain) has undergone scientific review at NIH and is being prepared for the IND application. To recruit patients suffering from Morton's neuroma, we established a collaboration with a regional network of podiatrists. They are also providing neuroma samples from surgical excision enabling evaluation of molecular markers within the neuroma using immunostaining and next-generation RNA-sequencing. We are optimistic that this layered approach to a distinct neuropathic pain condition will provide new insight into treatment mechanisms which might be translatable to other chronic pain indications, especially neuropathic pain conditions.

Session 3: June 2, 12:05pm

Brain Extracellular Matrix Biomechanics Is Associated With Altered Glial Plasticity in the Context of Chronic Pain

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Objective*:* Our main objective was to study hippocampal glial abundance and morphology and their relationship to the extracellular matrix in the context of peripheral trauma.

Specific Aims: Using the *in vivo* tibia fracture model of painful peripheral trauma in addition to the *in vitro* cell culture model in BV2 microglial cells, we aimed to:
1. Quantify hippocampal microglial and astrocytic abundance and morphology during the time course of injury (1, 3, 7, and 20 weeks after fracture).
2. Understand the relationship between extracellular matrix rigidity and glial survival/morphology/function.

Background: Chronic pain is characterized by changes in nociception, affect, and cognition, and is often resistant to classical treatment partly due to comorbid maladaptive plastic changes in the central nervous system. Specifically, a role for the hippocampus has been proposed due to its involvement in cognition and memory as well as in modulating the overall pain experience. Neuroinflammation has been demonstrated both in inflammatory and neuropathic models of pain where microglial and astrocytic numbers were increased in the rat hippocampal dentate gyrus 3 weeks after spinal nerve ligation and microglial activation was observed at 3 and 7 weeks following the peripheral administration of Complete Freund's adjuvant. In addition to hippocampal cellular plasticity in chronic pain, we have recently shown a key role for the hippocampal extracellular matrix in regulating pain and memory following peripheral injury. While these findings are novel and paradigm-shifting, we know little about how these extracellular changes are linked to glial abundance, morphology, or function.

Results and Significance: Male C57BL/6J mice ages 12–14 weeks were randomly divided to the injured (tibia fracture under anesthesia) and control (anesthesia only) groups. Behavioral measures of mechanical sensitivity (von Frey) and cognition (Y maze, social memory test) demonstrated injured mice to have decreased mechanical thresholds in the ipsilateral paw as well as deficits in working and long term memory. Analysis of hippocampal neuroinflammation (immunohistochemical staining of Iba1 and GFAP) demonstrated increased glial abundance starting at the 3-week time point. Sholl analysis indicated changes in the length and complexity of glial processes.
In order to study the influence of the extracellular matrix on glial survival, morphology, and function, we cultured BV2 microglial cells on artificial collagen matrices of varying rigidity (0.2kPa, 0.5kPa, and 2kPa). Quantification of cell survival and function (bead engulfment) both showed increases in the 2kPa condition. Sholl analysis of BV2 cellular processes is ongoing. Neuroinflammation supports many important persistent changes after injury including the release pro-inflammatory cytokines, chemokines, complement proteins, proteinases and reactive oxygen species which, in the context of the hippocampus, can be responsible for the chronification of pain and pain-related cognitive decline. Understanding the cellular and extracellular mechanisms of brain neuroinflammation is key to understanding pain mechanisms and identifying therapeutic targets. This approach goes beyond examining nociceptive pathways themselves and addresses structural factors supporting both pain and its related consequences.

My Pelvic Plan: An Integrative Intervention for Chronic Pelvic Pain

Sara R. Till, MD, MPH; Sawsan As-Sanie, MD, MPH; David Williams, PhD; Daniel Clauw, MD

Objective: To develop a web-based, self-management program for patients with CPP and to conduct a pilot randomized controlled trial to evaluate preliminary effectiveness of the intervention and phenotypic factors that predict positive response

Specific Aims:
Aim 1: To develop a web-based, integrative self-management program for patients with chronic pelvic pain
Aim 2: To conduct a pilot randomized controlled trial to evaluate preliminary effectiveness of incorporating this program into standard specialized care for chronic pelvic pain

Aim 3: To explore phenotypic factors associated with response to this intervention

Background: Chronic pelvic pain (CPP) is extremely common, affecting 15-20% of women. Pain and suffering often persist despite treatment, and lead to decreased productivity and reduced quality of life. The limitations of current surgical and pharmacologic treatments for CPP have been well documented.

One of the most significant clinical challenges in CPP is predicting which treatment is likely to be effective for an individual patient, due in large part to the heterogeneity of CPP. Management of other chronic conditions has improved with development of clinical phenotypes, which help clinicians more quickly match patients with effective treatments. However, clinical phenotypes have not yet been extensively explored in CPP.

Cognitive Behavioral Therapy (CBT), physical therapy, acupressure, and physical activity interventions have been shown to be effective in a wide range of chronic pain conditions. Among patients with CPP, several small studies have demonstrated efficacy of CBT, physical therapy, acupressure, and physical activity interventions. Effect sizes of individual non-pharmacologic interventions are typically small (0.15-0.3). However, interventions that integrate several of these modalities appear to have substantially improved efficacy (0.3-0.8), indicating possible synergistic rather than additive effects.

Web-based self-management programs help to reduce barriers to access, and many have been shown to be as effective as traditional face-to-face interventions. Our project will build upon Fibroguide, a successful web-based cognitive/behaviorally-focused self-management program for fibromyalgia. Patients with fibromyalgia demonstrated improvements in pain (0.64) and physical function (0.38) utilizing Fibroguide compared to usual care.

Results and Significance: Development of the preliminary web-based program has been completed. We will be conducting focus groups in coming months to refine the program. Following revision, we will begin recruitment for the pilot randomized controlled trial phase of the study.

Our overall hypothesis is that patients with CPP who participate in this program will demonstrate improvements in pain, physical function, health-related self-efficacy, and quality of life with this integrative self-management approach. Additionally, we believe that this program will help to address barriers that many patients with CPP frequently encounter, including limited availability of providers particularly in underserved areas, lack of insurance coverage, and high out-of-pocket costs.

Mitchell Max Award Finalists

Genomic Pathways Enriched by Differentially Methylated Genes are Linked to Racial Disparities in Chronic Low Back Pain

Edwin N. Aroke, Ph.D., CRNA, FAAN, **&** Burel R. Goodin, PhD

Objective: To examine DNA methylation profiles associated with racial disparities in non-specific chronic low back pain (cLBP).

Specific Aim(s):
Identify differentially methylated loci (DML) between non-Hispanic Blacks (NHBs) and non-Hispanic Whites (NHWs) with non-specific cLBP.
Examine interactive race by cLBP status differences in DNA methylation comparing NHBs with cLBP vs. NHBs pain-free controls (PFCs), NHW with cLBP vs. NHW PFCs, and race by cLBP interaction effect.
Compare functional genomic pathways enriched by DML annotated genes.

Background: Chronic low back pain (cLBP) is a major problem in the United States (US). Approximately 85% of individuals with cLBP have non-specific cLBP, meaning pain that lasts 12 weeks or longer and is not caused by a known pathoanatomical condition. While cLBP affects all segments of the population, individuals in the US who are racialized as non-Hispanic Black (NHBs) experience more frequent, severe, and disabling cLBP than other racial groups, particularly non-Hispanic Whites (NHWs). Evidence suggests that psychosocial conditions such as chronic stress due to discrimination or low socioeconomic status may contribute to racial disparities in pain. However, since race is a social construct, the biological mechanism by which social experiences cause worse cLBP for NHBs remains unclear.
Epigenetic modifications, such as DNA methylation, are mechanisms by which environmental exposures regulate gene expression. These experience-dependent changes in gene expression have been observed in individuals who have endured early life stress. Our previous works identified differential methylated genes and functional pathways associated with cLBP.

These and other studies suggest DNA methylation's role in racial disparities in cLBP and warrant a deeper exploration at the epigenomic level. Therefore, we examined epigenome-wide differences between NHBs and NHWs with non-specific cLBP.

Methods: 49 NHBs and 49 NHWs (49 cLBP and 49 PFC) with a mean age of 44.6 ± 12.8 years participated. Genomic DNA was extracted from blood samples and analyzed using reduced representation bisulfite sequencing (RRBS). We used limma and ingenuity pathway analyses to identify differentially methylated loci (DML; methylation differences of least 10% and $p < 0.0001$) and functional pathways, respectively.

Results and Significance: NHBs experienced more severe cLBP than NHWs ($p < 0.001$). After controlling for age and sex, we identified 2873 DML between NHBs and NHWs with cLBP. The DMLs annotated to 1695 genes, many of which have been implicated in various pain conditions. The annotated genes enriched pathways of relevance to pain, including corticotropin-releasing hormone signaling, dopamine-DARPP32 feedback in cAMP signaling, GABA receptor signaling, opioid signaling, and neuronal differentiation (e.g., synaptogenesis signaling pathway, calcium signaling, axon guidance signaling, and endocannabinoid neuronal synapse.

We examined DML within each race group to further investigate the race and cLBP interaction, comparing cLBP versus PFCs. We identified more DML, annotated genes, and functional pathways in NHBs than NHWs. The race by cLBP status interaction analysis revealed 191 DML, which annotated 160 genes and enriched 34 functional pathways, including axon guidance, endocannabinoid neuronal synapse, and RHOGDR signaling pathways.

These analyses revealed the enrichment of pathways that play a role in inflammation and stress dysregulation. Interestingly, the pathways implicated in chronic stress, including the corticotropin-releasing hormone and dopamine-DARPP32 feedback in cAMP Signaling pathways, are more significant in NHBs. Also, the most significant pathways in NHWs are related to inflammatory processes (e.g., notch signaling, role of JAK family kinases in IL-6-type cytokine signaling, and IL-22 signaling). Together these data suggest that DNA methylation may regulate gene expression in pathways of relevance to pain and stress. While additional studies are needed to verify this link, this work provides a preliminary understanding of how stressful live experiences such as racism can result in worse pain for NHBs.

Ideal Dose and Duration of Exercise Interventions to Achieve Treatment Response: An Individual-Participant Data Network Meta-Analysis Assessing the Comparative Effectiveness of Mind-Body Interventions for Knee Osteoarthritis

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Background: Knee osteoarthritis (OA) affects >42 million people in the US, and is a leading cause of long-term pain and disability with substantial healthcare costs. Given the lack of effective disease-modifying treatments for knee OA, its management is focused on amelioration of clinical symptoms mainly pain and function. The existing pharmacological treatments often have inadequate efficacy, and are associated with significant toxicities. Recently, mind-body interventions (Tai Chi and yoga) were recommended as core treatment options along with exercise-based interventions (physical therapy and exercise) in the multimodal management of knee OA. However, due to a limited evidence base, current guidelines are unable to offer recommendations for the sequence of such therapies, or how they can be tailored to individual patients. The optimal dose and duration of these interventions to elicit a treatment response remains unclear and the factors associated with treatment response to these interventions are not well understood.

Specific aims: In this study we examined (1) the comparative effectiveness of mind-body interventions (Tai Chi and yoga) vs. exercise-based interventions (physical therapy and exercise) for knee OA; (2) identified the factors associated with treatment response; and (3) identified the ideal dose and duration of exercise interventions which would elicit a treatment response.

Methods: RCTs evaluating effectiveness of Tai Chi, or Yoga compared with Physical Therapy, Exercise, Attention Control, and Usual Care were selected. Aim 1: Primary outcomes were pain and function (0-100). Individual participant data was synthesized and a single-stage network meta-analysis using mixed-effect linear regression models accounting for clustering in the individual studies was performed. Aim 2: Treatment response was defined using the OMERACT-OARSI responder criteria. Association between baseline demographics, pain and function, and dose and duration of interventions with treatment response using univariate and multivariable analysis was investigated. Mixed-effect logistic regression models accounting for clustering in the individual studies were used. Aim 3: Duration of intervention was categorized into 3 intervals (6-8, 10-12, and >12 weeks). Dose of the intervention was categorized based on total amount of exercise per week (<60, 60-120, and >120 minute/week).

Results: Eleven studies (1099 participants, mean age 65 years, 67% female, 63% white, 23% Asian) provided data. Aim 1: For pain, all interventions were statistically significantly better than usual care. Tai Chi was the most effective intervention (Mean Difference: 21.89, 95% Confidence Interval: 16.06, 27.71). Yoga (17.59 [13.22, 21.82]) was comparable to Physical Therapy (17.43 [11.03, 23.82]) and superior to Exercise (4.90 [1.50, 8.22]). Tai Chi (19.99 [12.88, 27.11]) was the most effective intervention in improving the function. Yoga (17.59 [13.22, 21.82]) and Physical Therapy (17.43 [11.03, 23.82]) had similar benefits on function compared to usual care. Aim 2: 41% of the participants responded to their treatment. On multivariable analysis, after adjusting for the intervention effect, only BMI (Odds Ratio 1.04 [1.02, 1.07]), and physical function (1.11 [1.02, 1.20]) remained significantly associated with treatment response. For every 10-point improvement in function the chance of treatment response goes up by 11%. Aim 3: After adjusting for age, gender, race, BMI, baseline pain and function, and the treatment, 10-12 weeks of exercise has >6 times odds of achieving treatment response compared to 6-8 weeks of intervention (Odds Ratio 6.30 [2.48, 16.05]). A 60-120 minutes/week dose of exercise was associated with 5 times higher odds of eliciting treatment response (5.05 [1.50, 16.87]) compared to >120 minutes/week of exercise.

Conclusions and Significance: Mind-body interventions produced beneficial effects similar or superior to those of standard physical therapy and exercise in the treatment of knee OA. Individuals with lower BMI and those with better baseline physical function are more likely to respond to exercise-based interventions for knee OA. A 60-120 minutes/week of exercise for 10-12 weeks is the ideal dosage and duration to elicit a treatment response in individuals with knee OA. Our findings are more generalizable owing to our large sample size and inclusion of individuals from multiple countries worldwide. These results may help clinicians optimize patient-centered exercise treatments and better manage patient expectations. Standardized mind-body interventions should be considered as effective therapeutic options for knee OA, highlighting the importance of the holistic wellbeing of the individuals.

Visualizing Transformations of Spinal Sensory Coding in Neuropathic Pain

David A. Yarmolinsky, Caitlin Greene, Yu-Ting Cheng, Seungwon Choi, David D. Ginty, Clifford J. Woolf

Background: Signals for temperature, crude touch, itch, and pain enter the brain via the anterolateral tract (ALT), a projection originating primarily in the superficial dorsal horn and terminating in diverse hindbrain and thalamic targets. In pathological states such as peripheral neuropathic pain, changes in function of spinal and peripheral somatosensory circuits contribute to modifications of organismal responses to both noxious and normally innocuous stimuli. Longitudinal measurement of stimulus-response properties in transcriptionally and anatomically defined neurons of the superficial dorsal horn has the potential to provide a rich readout of circuit function and dysfunction in the context of a spared nerve injury, a well characterized model of chronic peripheral neuropathic pain. We therefore developed and applied a chronic *in vivo* calcium imaging methodology to characterize functional plasticity of the spinal dorsal horn at cellular resolution.

Objective: To identify how the cellular representation of thermosensory information within the superficial dorsal horn is altered across the transition from a nociceptive to a neuropathic pain state.

Specific Aims:
Aim 1: Establish methods for long-term *in vivo* calcium imaging of neurons in the dorsal horn of mice.
Aim 2: Identify alterations in spinal sensory representations associated with neuropathic pain by generating longitudinal cellular-scale maps of temperature-evoked activity prior to, during, and after induction of spared nerve injury.

Results: We implanted mice with 3D printed spinal windows providing stable optical access to lumbar dorsal horn for >3 months, and targeted GCaMP6f expression to anatomically defined ALT neurons by retrograde labeling from the lateral parabrachial nucleus, and to molecularly defined populations defined by expression of $Gpr83^{creER}$ or $Tacr1^{creER}$. We mapped activity evoked by thermal and mechanical stimulation of the hind paws in the basal nociceptive pain state, finding that responses to thermal stimuli are normally segregated into functionally distinct classes of neurons tuned to cooling, innocuous warming, or noxious heat. These stimulus-evoked population responses are stable for weeks prior to injury and are conserved across awake and anesthetized conditions. Induction of spared nerve injury results in rapid, widespread, and sustained reorganization of thermosensory maps mediated by stereotyped changes in sensory tuning. Polymodal and high-threshold thermal responses are substantially expanded through recruitment of previously unresponsive cells and loss of selectivity in cold-sensing neurons. Conversely, we observe a profound and sustained loss of function in cells tuned to innocuous warming and a transient loss of cold-selective responses. Importantly, these transformations occur on multiple time scales ranging from minutes to weeks after injury, necessitating longitudinal imaging to faithfully capture dynamics. In ongoing work, we are investigating parallel changes in mechanosensory representations and stimulus-uncoupled activity associated with the neuropathic pain state.

Significance: Aberrant patterns of neural activity within the somatosensory systems are a key feature of maladaptive pain states and proximal cause of clinically relevant pain disorders. By directly visualizing neuronal ensemble activity in the dorsal horn, this study identifies cellular populations with altered function between nociceptive and neuropathic sensory circuits that may serve as targets for therapeutic intervention. This approach will be broadly applicable to clarify mechanisms of sensory dysfunction in clinically relevant acute and chronic pain models.