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TITLE: Biopsychosocial Mechanisms of Chronic Pain Recovery and Maintenance

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## Introduction

### **Chronic Pain, Its Impact in the US Military, and Its Burden in the Veterans Administration**

Chronic pain and opioid misuse are economically costly, impair optimal military readiness, and lead to an ever-increasing loss of life. An estimated 44% of recently deployed active-duty service members have a chronic pain condition. When not engaged in combat, almost one-third of deployed service members sustain a non-battle injury, many of whom require medical evacuation. In Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND), service members medically evacuated due to musculoskeletal and connective tissue disorder-related pain (e.g., joint pain, low back pain, osteoarthritis) or combat-injuries were less likely to return to duty than those evacuated with other conditions. These medical evacuations represent a small fraction of chronic pain experienced by deployed service members. In a non-treatment seeking sample, almost half (44%) of recently returned combat-deployed service members had chronic pain (lasting >3 months) and 15% reported past-month opioid use. Of those reporting pain, approximately half described pain as lasting longer than a year, occurring nearly daily or constantly, and/or having moderate to severe intensity. Chronic pain prevalence is increasing among OEF/OIF/OND veterans and likely to become more common as veterans age. As a result, the impact of chronic pain is magnified within the Veterans Administration (VA) and more than half of all patients have a chronic pain condition. Moreover, the prevalence of chronic pain among service members and veterans is significantly higher than in civilian populations. Coinciding with chronic pain among service members and veterans, opioid use and subsequent misuse further adds to pain-related morbidity. To reduce the iatrogenic effects of opioid therapy, reduce the incidence and impact of chronic pain, and improve quality of life among service members and veterans, it is essential to carefully examine the biopsychosocial processes by which chronic pain resolves. In doing so, novel pharmacological therapeutics, non-pharmacological approaches, and pain treatment sequences can be efficiently developed.

### **Biomarkers and Biological Substrates of Pain Chronification**

Both animal and clinical studies indicate that variations in protein expression can identify who is at risk for the development and maintenance of chronic pain, representing a promising direction of future therapeutic developments. We at the Medical Readiness Systems Biology (MRSB) branch at Walter Reed Army Institute of Research (WRAIR) have been employing state-of-the-art multi-omics technologies and computational biology approaches for data analysis, data mining, knowledge integration, hypothesis building and product development for several years, all aimed at improving the detection, diagnosis and treatment of illnesses of military relevance. We have published findings on identification of molecular signatures for complex conditions and disease states (biomarkers) ranging from psychological illnesses to biothreat agent exposure. In the current project, we will be looking at microRNA biomarkers for predicting chronic pain and recovery

### **Framing Chronic Pain and Its Mechanisms within an Evidence-Based Model**

The experience of pain is multidimensional and dynamic, with individual variation in presentation, chronification, and resolution. Identifying mechanisms that sustain and resolve chronic pain can enable optimized chronic pain management and novel therapeutic development. To best identify these mechanisms, the biopsychosocial model provides an effective framework for understanding pain chronification, maintenance, and recovery. The model's evidence-based framework contextualizes the patient experience by identifying biological, psychological, and social factors related to chronic pain. To bolster the biopsychosocial model in understanding chronic pain mechanisms, the four-stage model of pain chronification provides a helpful roadmap in identifying dynamic processes.

### **Potential Mechanisms of Chronic Pain Recovery and Resolution**

Chronic pain treatment may halt or reverse the biopsychosocial processes associated with pain chronification at all four stages (predisposition, injury/acute pain experience, transition, maintenance), by enhancing emotion regulation, modulating attentional processes, and changing conditioning patterns. Given that effective chronic pain treatments appear to reverse the processes set forth by pain chronification, the biomarkers underlying pain chronification may also be helpful to identify and understand pain resolution and develop targeted treatments focused on these processes. In addition to conducting multidimensional assessment to capture the full biopsychosocial experience of chronic pain maintenance and recovery, optimal assay sensitivity is required for biomarker studies. As such, chronic pain maintenance and recovery must be defined in a patient-centered and pragmatic manner, reflective of the actual human experience.

### **Capturing Chronic Pain Recovery and Maintenance in a Patient-Centered Approach**

As noted in the above section, a systems biology approach accounts for the complexities of the

physiological experience. Given the interrelationships between biological, psychological, behavioral, and social factors in pain chronification, maintenance, and recovery, it is also useful to assess a wide range of functioning domains as well.

### **Specific Aims:**

To optimize Chronic Pain Management, this proposed study seeks to understand the mechanisms that sustain or resolve chronic pain within a biopsychosocial framework. The objective of the present study is to identify biopsychosocial markers of chronic pain maintenance (Maintained) and recovery/improvement (Improved). The specific aims of this study are:

#### **Aim 1: To identify baseline (a) biomarkers and (b) psychosocial/behavioral factors uniquely associated with group membership (Controls, Maintained, Improved), then explore their interrelationships.**

Hypotheses: (a) There will be significant differences in biomarker expressions, such that various biomarkers will distinguish each group from one another. (b) Participants in the Improved group will report lower baseline depression, anxiety, anger, fatigue, sleep-related impairment, pain catastrophizing posttraumatic stress, alcohol use, prescription pain medication misuse, and morphine equivalent daily doses, while reporting higher social role satisfaction compared to the Maintained group. The Improved and Maintained group will have higher baseline levels of depression, anxiety, anger, fatigue, sleep-related impairment, and pain catastrophizing than the Control group. Exploratory: Correlations will assess the relationships between the identified biomarkers and psychosocial/behavioral factors associated with group membership.

#### **Aim 2: To identify (a) biomarker and (b) psychosocial/behavioral factor changes (baseline to ~6-week follow-up) uniquely associated with Maintained versus Improved group membership, then explore their interrelationships.**

Hypotheses: (a) Baseline to ~6-week changes in unique biomarker expressions will distinguish the Maintained and Improved groups from one another. (b) The Improved group will report greater baseline to ~6-week improvements in depression, anxiety, sleep-related impairment, and pain-catastrophizing compared to the Maintained group. Exploratory: Correlations will assess the relationships between the identified changes in biomarker expression and psychosocial/behavioral factors associated with group membership.

#### **Aim 3: To identify salivary biomarker correlates of plasma biomarkers associated with chronic pain maintenance and recovery/improvement.**

Hypotheses: Significant blood-based baseline biomarkers and biomarker changes identified in Aim 1 will have corresponding salivary biomarkers.

**Keywords – Chronic pain, biomarkers, microRNA, integrative pain management**

### **Accomplishments**

- Milestone 1: Gain IRB approval :U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) (HSD-19-04) was transferred as WRAIR #2665 after U.S. Army Center for Environmental Health Research's (USACEHR) transition to WRAIR. The PI at WRAIR is Dr. Rasha Hammamieh.
- Milestone 2: An agreement between DVCIPM and WRAIR is at final stages of approval.

#### **Future Milestones:**

- Milestone 3: Sample procurement, processing, data analysis and interpretation.
- Milestone 4: Manuscript on the biological biomarkers of chronic pain and recovery recovery.

### **Impact**

*Nothing to Report*

## **Changes/Problems**

The COVID19 Pandemic is likely to have a large impact on the timeline of this study, not only for obtainment of samples, but also the continued progress on other study aims and goals.

**Products** – None to report

## **Participants & Other Collaborating Organizations**

Name: Krista Highland  
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Nearest person month worked: 1.8  
Contribution to Project: no change

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Contribution to Project: HRPO initial approval (USAMRICD)

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Contribution to Project: Agreement paperwork and HRPO transition to WRAIR

**Special Reporting Requirements** – n/a

## **Appendices**

*Nothing to Report*