Title: Characterization and Treatment of Chronic Pain after Moderate to Severe Traumatic Brain Injury.

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Background. After a traumatic brain injury (TBI), a large number of individuals experience chronic pain (i.e., pain that lasts at least three months) that may or may not be directly related to the TBI. Over 70% of non-military individuals and 80% of active military and veterans have reported chronic pain after TBI. Living with chronic pain impacts almost all aspects of a person's life: physical function, concentration and memory, sleep, and feelings of depression, anxiety and irritability. It has been difficult to identify effective treatments because large studies of individuals with TBI and chronic pain have not been conducted. This study will leverage an existing successful research network (TBI Model Systems – TBIMS) that has the largest number of individuals with TBI who have been enrolled and followed in a well characterized, long-term database related to TBI. The aims of this study are to: 1) Determine chronic pain classification (musculoskeletal, headache, central/neuropathic), prevalence, location, duration, and associations with demographic, injury severity, current level of functioning and comorbidities in participants followed in 10 centers participating in the National Institute on Disability, Independent Living and Rehabilitation Research and the Department of Veterans Affairs TBIMS databases; 2) Identify extreme groups based on responses to pain (interference and perception of improvement with treatment), or chronic pain extreme phenotypes, in order to define the key differences between those who have a good outcome and those who do not, across factors related to injury, pain severity/location, demographics, and treatment history; and 3) Identify treatment practices by clinicians who treat comorbid TBI and chronic pain to determine gaps in availability/accessibility of guideline level treatment, highlighting underserved populations where applicable.

The study aims of this 5-year observational cohort study of individuals with moderate to severe TBI enrolled in the NIDILRR and VA TBIMS are to:
Aim 1 (Chronic Pain Characteristics and Associations). Determine chronic pain classification (musculoskeletal, headache, neuropathic (central)), prevalence, location, duration, and associations with demographic, injury severity, current level of functioning, and comorbidities in participants followed in the TBIMS National Database (NDB).
1.1. What is the type, prevalence, location, and duration of chronic pain in individuals with TBI?
1.2. What are the associations between chronic pain characteristics and (a) TBI factors (e.g. severity, closed vs penetrating, cause); (b) patient factors (b1) demographic factors (e.g., gender, age, education), (b2) comorbid conditions (e.g., PTSD, depression, anxiety, sleep, substance use), (b3) personal factors (coping, self-efficacy); and (c) treatment history (e.g., exposure to pain treatment).

***Aim 2** (Phenotypes)*. Identify and compare chronic pain extreme phenotype characteristics across two outcomes – impact of chronic pain on daily life and overall perceptions of improvement.

2.1. Define subgroups of participants with extreme responses (i.e., best and worst outcome) across two pain outcomes: (1) chronic pain impact on daily life (*Brief Pain Inventory* (BPI)60 pain interference scale), and (2) overall perception of improvement (*Patient Global Impression of Change Scale* (PGIC)61).

2.2. Compare extreme responders defined by best and worst outcomes using pain impact and perceived improvement on (a) TBI factors (e.g. severity, closed vs penetrating, cause); (b) pain factors (type, intensity, location, duration); (c) patient factors (c1) demographic factors (e.g., gender, age, education,), (c2) comorbid conditions (e.g., PTSD, depression, anxiety, sleep, substance use), (c3) personal factors (coping, self-efficacy); and (d) treatment history (pain treatment exposure) to develop extreme phenotypes.

***Aim 3** (Health Services)*. Identify treatment practices by clinicians who treat comorbid TBI and chronic pain to determine gaps in availability/accessibility of multidisciplinary pain treatment, highlighting underserved populations where applicable.

3.1. What is the range of treatment practices and typical referral patterns for individuals with TBI with chronic pain?

3.2. What are the facilitators and barriers to evidence-based treatments (comorbidities, interpersonal skills, etc.)?

Study population and setting (Aims 1-2). Persons with moderate to severe TBI who are already enrolled in the TBIMS NDB from one of the participating TBIMS Centers will comprise the study population. This study anticipates successfully recruiting 3,800 participants with TBI across all follow-up years (1, 2, 5, 10, 15, 20, 25, 30 years post injury). Participating TBIMS Centers include civilian NIDILRR-funded TBIMS sites: Craig Hospital, Englewood (CO); Rehabilitation Hospital of Indiana, Indianapolis (IN); Spaulding Rehabilitation Hospital Network, Boston (MA); Rehabilitation Institute of Michigan/Wayne State University, Detroit (MI); Mayo Clinic, Rochester (MN); Rusk Rehabilitation, New York (NY); Baylor Institute for Rehabilitation, Dallas (TX); Virginia Commonwealth University, Richmond (VIR); and University of Washington, Seattle (WA), University of Alabama, Birmingham (AL); TIRR Memorial Hermann, Houston (TX), and and one VA TBIMS site, James A. Haley Veterans Hospital, Tampa (FL), which is the VA TBIMS center with the largest enrollment and follow-up numbers. The jointly funded TBIMS databases are the largest civilian and military longitudinal study in the world following individuals who receive inpatient rehabilitation for TBI. All individuals with TBI admitted to inpatient rehabilitation and meeting inclusion criteria for the TBIMS NDB are approached for consent and participation.

Study population and setting (Aims 3). In years 2 and 3, focus groups will be conducted to identify the range of treatment practices and typical referral patterns for individuals with TBI with chronic pain. Up to 10 focus groups with up to 100 multidisciplinary rehabilitation providers who treat individuals with TBI and chronic pain to discuss current treatment practices and their perceived facilitators and barriers to implementing evidence-based treatments. Outcomes from this study will include educational materials on chronic pain and pain treatment

to benefit patients, family members, clinicians, and policymakers. Data from this study will have a direct impact on clinical practice, informing future work, and promoting understanding of constituent factors in extreme phenotypes.

Knowledge Translation Plan. Products from this study will focus on 1) informing professionals on current research findings, and 2) educating consumers/stakeholders. Stakeholders for this work include individuals with TBI, their families, clinicians who treat those with TBI, insurance providers, and policy makers. We plan to work with the NIDILRR-funded Model Systems Knowledge Translation Center (MSKTC) to provide scientific results and information for dissemination to researchers, clinicians, and policymakers, using a variety of mechanisms including professional meetings, webinars, Web sites, and through publications and the development of factsheets. Factsheets on chronic pain and its relationship to other co-occurring conditions, as well as treatment ideas, will be written for both professional and patient/family member audiences. We will also leverage the development of a fact sheet and infocomic on chronic pain that is currently being developed by the WA TBIMS to provide early information on current issues around chronic pain and its treatment to consumer audiences. The MSKTC has committed to assist in translating and disseminating evidence-based products to relevant audiences as well as conduct systematic reviews and develop evidence-based practice consumer products. In addition to our collaboration with the MSKTC, we will utilize the methods from each of the 10 sites involved to share information across sites through local websites, social networking, newsletters, and live events at each site within their usual mechanisms. This will also include presentations by site-investigators to their local TBIMS advisory boards to gather input and context for our findings. We will identify relevant professional organizations and/or meetings for primary care physicians, neurologists, and pain experts in order to provide them with relevant information from this study. We have heard from individuals with TBI that they are often expected to educate their non-rehabilitation providers (including primary care physicians) on the impact that their TBI can have on a presenting problem, therefore we believe it will be important to assist in educating those providing pain treatment to this population. Our Stakeholder Investigator will assist in identifying appropriate provider types and organizations to assist in this process.