

CENC Clinical Care Monograph #1

Summary of CENC performance period 2013-2019

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The 'Perspectives' and 'Clinical Pearls' expressed are based on interpretation of findings from the described Chronic Effects of Neurotrauma Consortium (CENC) research studies and their assimilation with the extant literature. These views are endorsed by CENC leadership but may vary across individual researchers. All findings involve Service Members (SMs), Veterans (Vs) or both.

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A. TBI and Co-occurring Conditions

Key Finding #1: CENC researchers found associations between traumatic brain injury (TBI) diagnoses and epilepsy,¹ hearing loss and tinnitus,² and other sensory disorders (e.g., visual, balance/dizziness).³ In all cases, the association was strongest for Moderate to Severe TBI, but still present for Mild TBI.

Perspective: The associations found between TBI and these other diagnoses are worrisome, especially for the common mild TBI; however, they should be considered tentative pending evidence from more rigorous, prospective, longitudinal studies.

Clinical Pearls:

- Regardless of epilepsy risk level, routine prophylaxis with antiepileptic medication is not warranted after TBI of any severity, with the possible exception of penetrating TBI.
- The care of SMs/Vs with TBI, even mild TBI, should include assessment for sensory problems, as identification is integral to facilitating positive long-term outcomes.

B. TBI and Neurodegenerative Conditions

Key Finding #2: CENC researchers found associations between TBI and Dementia,⁴ and Parkinson's disease (PD).⁵ The association was strongest for Moderate to Severe TBI, but still present for Mild TBI diagnoses. Estimates of overall risk for dementia following TBI are 4%-6%, while the risk for PD following TBI remains <1%. Evidence also suggests that dementia following TBI on average may occur 1-2 years earlier than for those without TBI.

Perspective: The associations found between TBI diagnoses and neurodegenerative disorders are concerning, especially for the common mild TBI, such that the risk of TBI-related neurodegenerative disorders should be taken seriously. The ongoing prospective, longitudinal, multicenter CENC study will yield more definitive evidence on the nature and degree of the link.

Clinical Pearls:

- The clinical care of SMs/Vs with prior TBI should include recognition and treatment of known modifiable, lifestyle dementia risk factors (e.g., diet, exercise, sleep, tobacco, alcohol/illicit substances, socialization).
- SMs/Vs with prior TBI, even mild TBI, should be monitored for PD and/or dementia. SMs/Vs should be referred for specialty evaluation when signs are present, even if SMs/Vs are a little younger than would normally be expected.

C. TBI, Pain, and Opioid Therapy

Key Finding #3: CENC analysis of TBI evaluations in the VA healthcare system showed that chronic pain and chronic pain disability were associated with TBI, PTSD and depression.⁶ Opioid prescribing patterns for pain management did not appear to differ substantially for Veterans with or without TBI. About 20% with TBI and pain received short-term opioid therapy, while 3% received long-term opioid therapy. About 90% of Veterans with TBI treated with long-term opioid therapy had moderate to extreme levels of pain, PTSD symptoms, and sleep disturbance; 80% received at least one non-opioid therapy first.

Perspective: Chronic pain symptoms co-occur with TBI and other disorders that make successful treatment challenging. While clinical guidelines recommend against prescribing opioids to Veterans with a history of TBI, opioid prescribing patterns do not differ between those with or without TBI. Of note however, only 3% of Veterans with TBI were treated with long-term opioids. Prospective longitudinal studies of the interplay between pain, TBI, and treatment approaches are needed.

Clinical Pearls:

- When disabling chronic pain in SMs/Vs with TBI is identified, clinicians should emphasize non-opioid treatments and use a person-centered care model.
- Opioid therapy should only be used under evidence-based guidelines.

D. Persistent Symptoms after mild TBI

Key Finding #4: CENC researchers found that a greater number of prior mild TBIs of any type (blast-related or non-blast) were associated with chronic, increased, widespread symptoms,^{7, 8} but not with decreased cognitive performance^{7, 9} among young to middle aged Vs/SMs.

Perspective: Associations between more concussions and higher symptoms are likely to be complex and multifactorial and need further research.

Clinical Pearls:

- The clinical standard of care for persistent symptoms after mTBI should follow a symptom-oriented approach (i.e., do not focus on “cause” or “diagnoses”).
- Clinicians should recommend a compensatory strategy approach to the treatment of self-reported memory or other cognitive difficulties after mTBI.

Key Finding #5: CENC researchers found that factors such as sleep, PTSD, and pain impacted cognitive performance after mTBI.⁹

Perspective: Cognitive performance can be lowered by a range of factors other than mild TBI history.

Clinical Pearl:

- The treatment of cognitive difficulties in SMs/Vs with prior mTBI should be holistic and address all comorbidities.

Key Finding #6: CENC researchers found that SMs/Vs with 3 or more mild TBIs had a small decrease in balance performance on computerized posturography.¹⁰

Perspective: There is an apparent cumulative 'dose effect' of mild TBI on balance performance that, although not large, may present a clinical problem for some SMs/Vs.

Clinical Pearls:

- Repetitive mild TBI should raise the index of suspicion for balance problems and potential need for treatment.
- Secondary TBI prevention strategies are increasingly important as the number of mild TBIs sustained increases in order to limit late effects of mTBI.

Key Finding #7: CENC researchers found that several other factors, in addition to prior mild TBI, were associated with poorer balance performance, with pain showing an especially strong relationship.¹⁰

Perspective: Balance performance is a delicate and complex process controlled by brain networks that integrate and process multiple afferent and efferent pathways. Pain can disturb this process by a number of potential central or peripheral mechanisms.

Clinical Pearl:

- The treatment of balance problems in SMs/Vs with prior TBI should address pain before and during vestibular rehabilitation or other interventions.

Key Finding #8: CENC researchers found that mild TBI history is not directly related to chronic pain. Factors found directly related to chronic pain were PTSD, Anxiety, Depression, Insomnia, Arthritis, and extracranial injuries.¹¹

Perspective: Chronic pain likely has a myriad of causes, contributing factors, with the role of mild TBI being unclear.

Clinical Pearl:

- Vs/SMs with chronic pain should receive holistic care, regardless of their mTBI history.

Key Finding #9: CENC researchers found that using MRI data, chronic pain is associated with decreased functional connectivity in certain brain networks.¹²

Perspective: Pain may disturb brain functioning through a spill-over effect.

Clinical Pearl:

- Modulation of brain networks through biofeedback or other means to reduce pain and improve brain function seems an appealing treatment approach, however more research is needed to formulate clinical recommendations.

Key Finding #10: CENC researchers found that blood levels of exosomal proteins, especially neuronal proteins (NFL, p-tau, tau) and neuroinflammatory proteins (IL-6 and IL-10), are associated with both mild TBI history and symptom levels in SMs/Vs.¹³

Perspective: In early discovery studies, exosomal proteins emerged as potential diagnostic or prognostic biomarkers of late effects of mild TBI, especially repetitive (≥ 3) mild TBI.

Clinical Pearl:

- While preliminary, these findings lend support to the clinical pearl that “secondary TBI prevention strategies are increasingly important as the number of mild TBIs sustained increase.”

Key Finding #11: CENC researchers repeated found that there were no differences in selected outcomes between blast-related and non-blast-related mild TBI, when adjusting for other factors such as PTSD, pain, depression, sleep.⁷⁻¹¹

Perspective: The extant literature is mixed, but largely in agreement with these CENC findings. Further research is needed to determine if blast-related, mild TBI requires different treatments or risk monitoring than blunt, mild TBI.

Clinical Pearl:

- SMs/Vs with clinical problems after mild TBI of any cause should receive symptom-based, holistic care regardless of the etiology of their mTBIs.

Key Finding #12: CENC researchers identified that the following factors were associated with missed study visits by SMs/Vs in clinical research; younger age, Hispanic ethnicity, PTSD diagnosis, and blast-related, mild TBI diagnosis.¹⁴

Perspective: Clinical research retention strategies should be tailored for the individual characteristics of the SMs/Vs, with extra attention directed towards participants who are of younger age, Hispanic ethnicity, PTSD diagnosis, and/or blast-related, mild TBI diagnosis.

Clinical Pearl:

- Individuals with mTBI who are of younger age, Hispanic ethnicity, PTSD diagnosis, and/or blast-related, mild TBI diagnosis have lower worse research study compliance and may also demonstrate reduced adherence to clinical treatments, so additional care should be applied to engage their full participation in care.

E. Disability Ratings and mild TBI

Key Finding #13: CENC researchers found differences in service-connected disability ratings¹⁵ and medical service use¹⁶ depending on elements of mild TBI history, specifically service-connected disability ratings and medical service use were highest for Vs with blast-related mild TBI, next highest for blunt mild TBI, and lowest for Vs without TBI.

Perspective: Vs with mild TBI appear to be utilizing the VA system for health care services as intended. Differences in clinical services received may confound outcome comparisons. Further prospective research is needed to better understand factors contributing to disability after mild TBI.

Clinical Pearl:

- To optimize functional status and life participation, Vs/SMs with mild TBI may need a rehabilitation approach in addition to a medical model of symptom and disease management.

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