

TBI Across the Lifespan



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Key Principles



- Understand the TBI specific acute and chronic somatic, cognitive and behavioral sequelae for the injury sustained.
 - Pre- and co-morbid conditions are major factors.
- Explore SOTA diagnostic and management principles for sequelae.
 - There is no place for idiosyncratic approaches.
 - Unproven and designer remedies should be avoided.
- Understand the inherent risks of long-term degeneration after TBI.
- Be aware of the efficacy of low-cost, community based services to optimize return to school, work and play.

Acute Care



- J.K. is a 45 yo male driver s/p MVC with GCS 8, while M.B. is a 17 yo passenger with GCS 14 .
- M.B. is seen in ED complaining of headache and dizziness, but noted to be stable and sent home with f/u.
 - What are next steps? Short term? Long term?
- J.K. is sent to ICU and evaluation day 2 reveals elevated ICP's (>30 mmHg), disorder of consciousness with localizing to the left.
 - What are next steps? Short term? Long term?

Acute Care



- **Acute management of concussion**
 - Reassurance on high likelihood of full recovery
 - Limited diagnostic testing other than history and exam
 - Early return to full activity (1-2 days), including school, work and exercise
 - Standard management of common symptoms
 - Referral for specialized care if slow results in 5-7 days
 - Monitoring of return to activity, but limited services needed
 - 3+ months of f/u
- **Acute management of moderate/severe TBI**
 - Neurosurgical/Imaging assessment
 - Preventative medical management
 - Early rehabilitative assessment (1-3 days) and care
 - Inpatient rehabilitation care as needed
 - Community, school and vocational reintegration
 - 12+ months of f/u

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Acute Concussion Care



- Approximately 4 million Concussions annually in the U.S.
 - <50% are seen by health care professional
 - Diagnosis is based on history
 - No acute role for imaging, neuropsychological evaluation or special diagnostics (90+ days post-injury).
 - Excellent chance of total functional recovery
 - Very small (<5%) risk of long-term limitations
 - Miniscule risk of long-term degeneration (CTE)
 - Recovery mediated by multiple factors
 - Patient (and clinician) expectations and biases
 - Time to return to full and normal activity
 - Persistence of symptoms despite treatment
 - Co-morbid conditions (pain, mental health, substance use)
 - Prior TBI and other neurological disorders

Acute Concussion Care



- Return to full (non-contact activity) by day 1-5 regardless of symptoms
 - Mobilization and cognitive stimulation are keys to recovery
 - Seek specialty care if symptoms present after 3-5 days.
 - Physical/Occupational therapy
 - Counseling
 - Educational Tutoring
 - No specific “brain” reason why individual should refrain from physical or cognitive activity with symptoms (no evidence it will affect recovery)
 - Recovery mediated by multiple factors
 - Patient (and clinician) expectations and biases
 - Time to return to full and normal activity
 - Persistence of symptoms despite treatment
 - Co-morbid conditions (pain, mental health, substance use)
 - Prior TBI and other neurological disorders

Acute Concussion Care



- Return to full (including contact) once individual can perform all of the tasks of the “job” and does not exhibit any evidence of persistent cognitive deficits (5+ days).
 - Somatic symptoms (including dizziness) are non-specific
 - Behavioral symptoms are due to wide range of factors
 - Cognitive deficits may also be due to a range of causes, but individual should not “RTD” until these are back to baseline or stable and safe.
 - No specific “brain” reason why individual should refrain from physical or cognitive activity with symptoms (no evidence it will affect recovery)
- Early (Day 1-3) return to exercise improves outcome.
- Early return to all, safe activities (cognitive, behavioral , physical) promotes enhanced outcomes

Chronic Concussion Care



- Concussion is a static event, but the persistent symptoms associated with the event may need management.
- Usually difficult to discern primary cause of symptoms, but there is NO reason to believe that the more closely tied to concussion the symptom is the more it will persist.
- Symptom management does NOT differ as a result of mTBI.
- The base rates in the U.S. population for the common sequelae of mTBI are high and approximate the mTBI population.
- Individuals with chronic conditions are best managed with a psychological support.

Chronic Concussion Care



- Supports for return to school, work, sports or duty are essential.
- Physician must consider all elements of injury, suitability of environment and role for return, persistence of symptoms, age, co-morbid conditions and the desires of the patient (family)
- While too early return may (temporarily) exacerbate symptoms, a delay may result in permanently increased disability.
- Existing RTD guidelines are NOT evidence-based
- School and workplace supports are effective and low cost

Chronic Concussion Care



- There is no substantive evidence that non-elite athlete or military have any increased risk for long-term degeneration.
 - Persistent symptoms (pain, dizziness, irritability) and associated conditions (PTSD, GAD, depression, chronic pain) are likely to lead to long-term worsening (? Role of actual mTBI)
 - Chronic Traumatic Encephalopathy (CTE) appears to be limited to ultra-high exposures with limited intervention.
- There are currently no reliable diagnostic for risk or presence of CTE/dementias, other than history and physical exam.
- Strategies to prevent or manage dementias should be universally recommended: regular medical care, treat underlying diseases (cardiovascular, diabetes, COPD), diet, exercise, meditation, social engagement, and maintaining productivity.

Acute Care



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Moderate TBI: Post-Traumatic Seizures



- Late PTS is present in 4-7% all TBI, nearly 20% rehab TBI, and 35-50% penetrating TBI patients.
- Early PTS is associated with increased risk late PTS
- 50-66% of individuals with late PTS will experience first seizure w/in 12 months.
- 75% of individuals with late PTS will experience first seizure w/in 24 months.
- PTS results in poorer short-term (physical and cognitive function) and long-term (vocational) outcomes after TBI.

PTS Prophylaxis



- 73% reduction in early PTS and 50% reduction in 1 year PTS in individuals given phenytoin for 1 week post-TBI.
- AANS and AAPM&R recommend 7 days of either PTH or CBZ post-TBI.
 - No proven benefits to giving prophylaxis >7 days post-TBI.
- Long-term challenges to PTS, so prevention vital
 - Driving
 - Work
 - Social
 - Psychological

DVT Prophylaxis



- All adult trauma patients admitted for >24 hours have at least a “Moderate” risk of DVT and require chemical prophylaxis by Day 1-2.
- DVT prophylaxis should continue until patient is ambulating to/from BR prn, appropriate time has passed, or returning home and continuing is not feasible.
- IVC or SVC filters are not appropriate DVT prophylaxis for any patient.
- One-third of patients with DVT will develop post-Phlebitic Syndrome (chronic pain and swelling).
 - Presents with long-term community integration and work issues.

DVT Management



- All DVT's (UE, Calf, w/IVC filter) should be treated for 3 months.
- All PE's should be treated for 6 months.
- Heparinization (LMWH or IV) should be given at least 5 days, check platelets on Day 3, then q3-7 days while on it.
- Coumadin should be delayed until 24 hours of heparinization is completed.

Hydrocephalus



- Maintain high index of suspicion, as plateau of progress may be the only sign.
- Head CT scan 1 month post-injury and then serially as warranted clinically.
- CSF tap or flow study for diagnosis if head CT is non-diagnostic.
- Consider ventriculostomy or V-P shunt.
- If persists, this will significantly adversely effect community and vocational integration.

Therapy Interventions



- Therapy (PT, OT, SLP) should begin by Day 1-3, depending on stability and availability.
- Protective helmet may required for cranioplasty (6-26 weeks).
- Full mobilization out of bed and controlled environment recommended.
- Partner with ICU nursing for carryover.
- Family involvement.
- Major prognosticators are duration of DOC and PTA.

NeuroEndocrine Management



- Clinically relevant NeuroEndocrine is uncommon after TBI, but should be screened for in severe TBI and individuals with slow recovery.
 - Thyroid function testing
 - Serum Sodium
 - Sex hormones
- Many of the common sequelae of TBI may mimic endocrine dysfunction (and vice versa)
 - Fatigue
 - Depression
 - Appetite dysfunction
- May significantly impact community integration and productivity.

Heterotopic Ossification



- **Diagnosis**

- High index of suspicion
- Clinical
 - ✦ Decreased and/or painful ROM
 - ✦ Swelling
 - ✦ Erythema
 - ✦ Warmth
 - ✦ Low-grade fever
- Imaging
 - ✦ Triple-phase bone scan
 - ✦ X-rays, late findings

- **Treatment**

- NSAID's
- Etidronate
- Controlled and aggressive ROM
- Often has negative long-term effects on community and vocational integration.
 - Loss of ROM
 - Pain

Spasticity



- Spasticity = Velocity dependent increase in resistance to stretch
- Tone = Resistance to stretch or movement
- Both are commonly seen signs of an upper motor neuron abnormality, that typically resolve as the lesion evolves
- Neither is inherently “bad” for the patient.
- Treatment should be initiated if the spasticity is limiting function, ROM, or is causing pain.
- Potential side effects of treatment must be weighed against potential benefits.
- Persistent spasticity can negatively affect community and vocational integration.

Pain Management



- Often overlooked or limited management for individuals with TBI.
- Pain is a common cause of TBI agitation and may worsen spasticity.
- Scheduled dosing of non-sedating agents (Tylenol, NSAID) are highly effective.
- If persists, this will significantly adversely effect community and vocational integration.

Cognitive Interventions: Hypoarousal



- No reliable data to support the efficacy of pharmacologic intervention in the vegetative or comatose patient.
- All you get is a very alert looking comatose patient.
- Research trials do support use of neurostimulants in “emerging” patients (RLAS III) -> Amantadine 300 mg/day, but effect is small.
- Once patient is >RLAS III, stimulant usage should be considered.
- If persists, this will significantly adversely effect community and vocational integration.

Cognitive Interventions: Hypoattention



- Managing diet, stimulation, sleep hygiene, environment and medication side effects are first line treatment.
- Neurostimulants have been demonstrated to improve attention and function.
 - Methylphenidate has the most clinically demonstrated efficacy for individuals who have progressed out of coma.
- If symptoms persist, this will significantly adversely effect community and vocational integration.

Cognitive Interventions: Agitation



- Agitation occurs in >50% of all TBI patients, however delirium, seizures, pain, and hypoxia can also manifest with agitation.
- True TBI agitation should be treated with environmental and behavioral interventions.
- Pharmacologic treatment should only be implemented in specific behaviors are identified and goals established.
- In the community, agitation is often labeled irritability, poor frustration tolerance or is masked by substance use.

Cognitive Interventions: Depression



- Depression occurs in up to 50% acute trauma patients. Vegetative symptoms are often hard to distinguish. Psychiatrists rarely have greater insight than treating MD's.
- Trial of Ritalin or SSRI is appropriate diagnostic tool. If true depression suspected, 6 months treatment indicated with switch to long-term agent.
- If persists, this will significantly adversely effect community and vocational integration.

Community Interventions



- Vocational rehabilitation (Supported Employment model) has been shown effective for TBI.
- Cognitive rehabilitation has been shown effective for 18+ months.
- Aerobic exercise has been shown to enhance symptom outcomes after concussion and for depression after TBI.
- Standard approaches for commonly occurring co-morbidities (pain, PTSD, depression) work after TBI

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The Chronic Effects of Neurotrauma Consortium (CENC)



CENC.RTI.ORG



Chronic Effects of Neurotrauma Consortium



CENC Overview

- Aligned to Presidential Executive Order 13625 and the National Research Action Plan
- \$62.175M of VA and DoD Funding awarded September 2013
- Oversight via Government Steering Committee with representation from VA, DoD, NIH, NIDILRR

Currently supporting 10 Studies Across Over 30 Participating Institutions*

VCU (Coordinating Center), Richmond VAMC, & University of Richmond

Barrows Neurological Institute

Baylor College of Medicine

Boston University & VAMC

Brigham Young University

Duke University

Fort Belvoir Community Hospital

Houston VAMC

Iowa City VA Health Care System & University of Iowa

Milwaukee VAMC

Minneapolis VAMC & University of Minnesota

Palo Alto VAMC

RTI International

Roskamp Institute & Tampa VA

South Texas Veterans Health Care System

San Antonio Military Medical Center

San Francisco VAMC & NICRE

University of California, San Francisco

Uniformed Services University of the Health Sciences

University of Washington

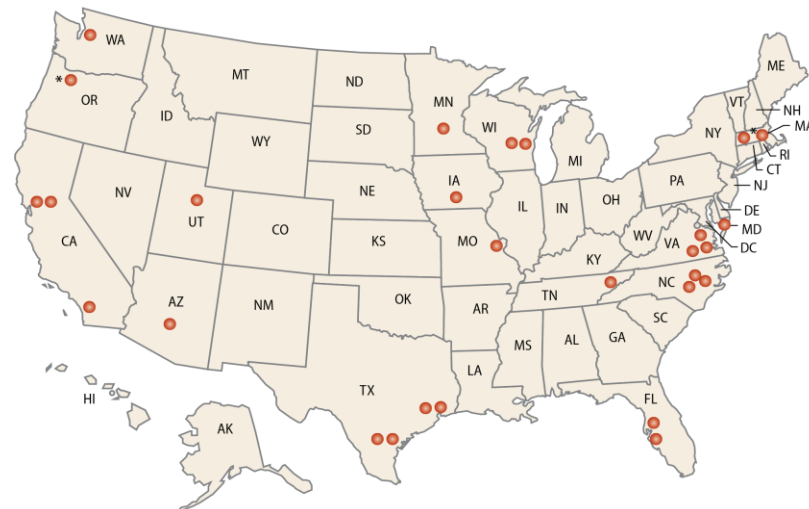
VA San Diego Health Care System

W.G. Hefner VAMC



CENC Sites

Barrows Neurological Institute, Phoenix, AZ
Baylor College of Medicine, Houston, TX
Boston University, Boston, MA
Brigham Young University, Provo, UT
Duke University School of Medicine, Durham, NC
Fort Belvoir Community Hospital, Alexandria, VA
Hunter Holmes McGuire VA, Richmond, VA
James A. Haley Veterans Hospital, Tampa, FL
Iowa City VA Health Care Center
Medical College of Wisconsin, Milwaukee, WI
Michael E. DeBakey VA Medical Center, Houston, TX
Milwaukee VA Medical Center, Milwaukee, WI
Minneapolis VA Health Care System
Mountain Home VA Medical Center, Mountain Home, TN
Northern California Institute of Research and Education, San Francisco, CA
Roskamp Institute, Sarasota, FL
RTI International, Durham, NC



San Antonio Military Medical Center, San Antonio, TX
San Francisco VA Medical Center, San Francisco, CA
South Texas Veterans Healthcare Center, San Antonio, TX
Uniformed Services University of the Health Sciences, Bethesda, MD
University of Missouri St. Louis, St Louis, MO

University of Washington, Seattle, WA
VA Boston Healthcare System, Jamaica Plain, MA
VA Palo Alto Health Care System
VA Portland Health Care System, Portland, OR
VA San Diego Health Care System, San Diego, CA
Virginia Commonwealth University, Richmond, VA
WG Hefner VA Medical Center, Salisbury, NC



Chronic Effects of Neurotrauma Consortium

Consortium Objectives

To establish the association (onset, prevalence, and severity) of the chronic effects of mild TBI (mTBI) and common comorbidities*

Determine whether there is a causative effect of chronic mTBI/concussion on neurodegenerative disease and other comorbidities*

Identify diagnostic and prognostic indicators of neurodegenerative disease and other comorbidities associated with mTBI/concussion

Develop and advance methods to treat and rehabilitate chronic neurodegenerative disease and comorbid effects of mTBI/concussion

Highlights

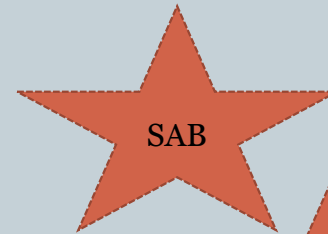
- Core facilities for common research efforts
- Alignment with DVBIC 15 Year Study for TBI
- Leverages
 - Multiple DoD and VA clinical sites
 - previously funded in-theater efforts for follow up data
 - DoD and VA Centers of Excellence
 - Nationwide expertise of established research networks
- Use of common data elements (CDEs) and entry of data into FITBIR
- Robust Peer Review Program to identify new projects

* Comorbidities include: psychological, neurological (memory, seizure, autonomic dysfunction, sleep disorders), sensory deficits (visual, auditory, vestibular), movement disorders, pain (including headache), cognitive, and neuroendocrine deficits

CENC

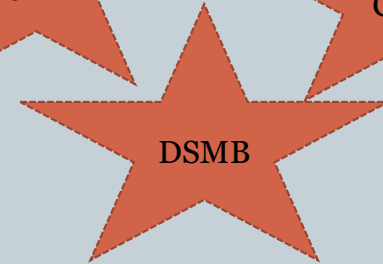


CENC Leadership
(VCU, USUHS,
RTI)



Consortium
Coordination
Center (VCU, RTI)

Peer Review
Program (VCU)



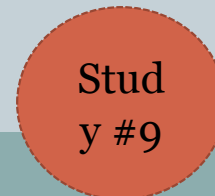
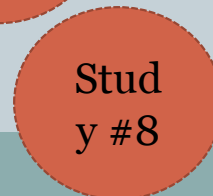
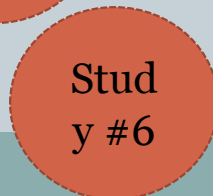
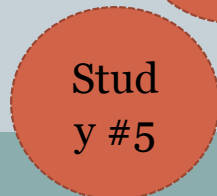
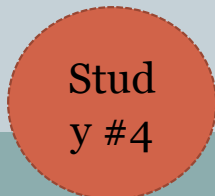
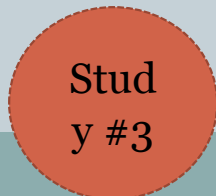
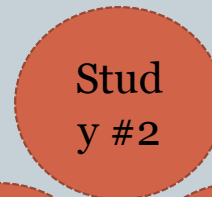
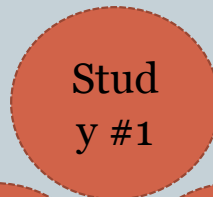
Biostatistics Core
(RTI)

Study and Data
Management Core
(RTI)

Biorepository Core
(USUHS)

Neuropathology
Core (Boston
VAMC-BUCM)

Imaging Core
(BCM)



CENC Oversight



- **Government Steering Committee (GSC)**
 - The GSC is the overall governing and management committee for the project through which the DoD/VA interact with the CENC.
- **Data and Safety Monitoring Board (DSMB)**
 - The DSMB provides independent scientific overview of data and study safety for all studies
- **Scientific Advisory Board (SAB)**
 - 12-member Board of non-CENC scientific leaders
- **Consumer Advisory Board (CAB)**
 - 10-member Board of stakeholders and persons served

CENC Study: Longitudinal



- **Observational Cohort Study on Late Neurologic Effects of Combat Concussion:**
 - William Walker, MD, Study PI (VCU)
- IRB approved and recruitment underway at 8 sites (Richmond, Houston, San Antonio, Tampa, Minneapolis, Portland, Boston VA's, Ft. Belvoir)
 - 880 subjects (2-13 years post-exposure) with combat exposure and mTBI, 220 with combat exposure alone
 - Comprehensive, in-person or telephone evaluation annually
 - Current subjects recruitment = 620

CENC Study: Tau Phosphorylation



- **Tau Modification and Aggregation in mTBI**
 - Elliott Mufson, PhD (Barrow) and Fiona Crawford, PhD (Roskamp), Study co-PI's
 - Animal colony created and intervention (repeated mTBI + stress) underway and tissue analysis laboratory established.
 - Aim is to develop an animal model of r-mTBI that will allow the tracking of progressive intraneuronal tau alterations that can be correlated with behavioral dysfunction, fluorescent in situ hybridization, and gene expression signatures and then be used to assess the effects of interventions.

CENC Study: Epidemiology



- **Epidemiology of mTBI and Neurosensory Outcomes**
 - Kristine Yaffe, MD, Study PI (UCSF/SF-VAMC)
 - Collaboration with SA-VAMC
 - Comprehensive integration and analyses of 9 VA, DoD and CMS healthcare system datasets with nearly 2 million unique subjects to study the chronic effects of mTBI on neurodegenerative disease and other comorbidities.
 - Seven manuscripts submitted

CENC Study: DTI Standardizations



- **Diffusion Tensor Imaging Standardization Using Novel MR Diffusion Phantoms**
 - Elizabeth Wilde, PhD, Study PI
 - Establishing standard DTI phantoms
 - Examines inter-scanner DTI differences in diffusion values using three types (an aqueous polymer solution, a micron-scale hollow fiber textile, and a hybrid of the two) of novel diffusion phantoms.
 - Goal is design of a standardized imaging protocol to provide optimal uniformity of diffusion.

CENC Study: Otolith Rehabilitation



- **Dysfunction and Postural Stability**
 - Faith Akins, PhD, Study PI (Mountain Home-VAMC)
 - Subject (n=124) recruitment underway
 - Assessing impact of specialized vestibular intervention vs. general rehabilitation intervention vs. control on subjects with balance deficits (+/- otolith dysfunction) due to combat-related mTBI
 - Computerized (Platform) Posturography is gold standard assessment tool.
 - Subjects recruited = 88

CENC Study: ADAPT



- **ADAPT**

- Christine MacDonald, PhD, Study PI (UW)
- Subject recruitment completed (n=94)
- 5 year follow-up using advanced MR imaging and clinical outcome measures of combat mTBI from Iraq-based ADAPT trial.
- Four groups studied;
 - Deployment mTBI from blast
 - Deployment mTBI from non-blast mechanisms
 - No mTBI but prior deployment blast exposure
 - No mTBI or deployment blast exposure.

CENC Study: Novel White Matter Imaging



- **Novel White Matter Imaging to Improve mTBI Diagnosis**
 - Amy Jak, PhD, Study PI (SD-VAMC)
 - Subject recruitment goal = 82, currently 32 recruited.
 - This study will use myelin-sensitive novel imaging techniques (mcDespot) to improve correspondence with diagnostic groups after trauma exposure and correlation with cognitive deficits in mTBI.
 - Three groups studied;
 - mTBI + PTSD
 - Isolated mTBI
 - Controls

CENC Study: Neurobiology



- **Structural and Functional Neurobiology of Veterans Exposed to Primary Blast Forces**
 - Katherine Taber, PhD, Study PI (Salisbury-VAMC)
 - Subject recruitment (goal =200); all OEF-OIF
 - 80 with primary blast TBI
 - 80 with blunt TBI
 - 40 without TBI
 - Diagnostics with advanced neuroimaging, structured interviews, cognitive testing and questionnaires.
 - Current recruitment = 52

CENC Study: Neurodegeneration



- **Clinical and Neuroimaging Correlates of Neurodegeneration**
 - Nick Davenport, PhD, Study PI (Minneapolis-VAMC)
 - Subject recruitment goal = 180
 - OEF-OIF Service Members and Veterans
 - Clinical interviews of psychopathology (SCID and CAPS) and TBI, self report measures of psychopathology (BDI, PC-M) and personality (MPQ, MMPI), neuroimaging (MRI, EEG) and blood-based protein expression.
 - Current recruitment = 48

CENC Study: Vision Sensory Impairments



- **Visual Sensory Impairments and Progression Following Mild TBI**
 - Randy Kardon, PhD, Study PI (Iowa City-VAMC)
 - Subject recruitment goal = 221; OEF-OIF Veterans
 - 146 with mTBI
 - 75 without mTBI
 - Testing therapeutic modalities: TMS, visual behavioral tasks, and peripheral and central nerve stimulation.
 - Recruitment at Minneapolis and Palo Alto VAMC
 - Current recruitment = 38

Thank You

