



“I Think I Have Chronic Traumatic Encephalopathy (CTE)”: A Clinician’s Guide to Managing a Research Phenomenon

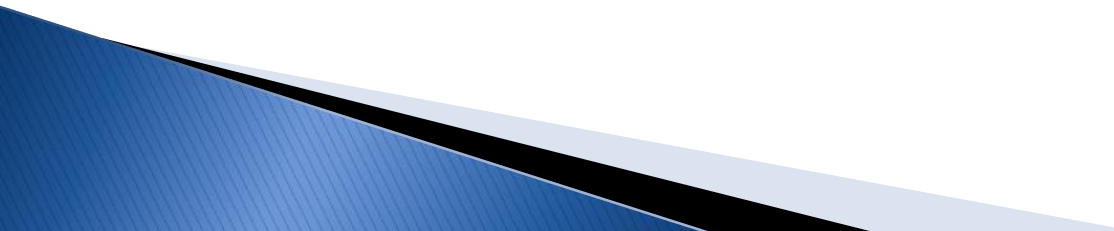
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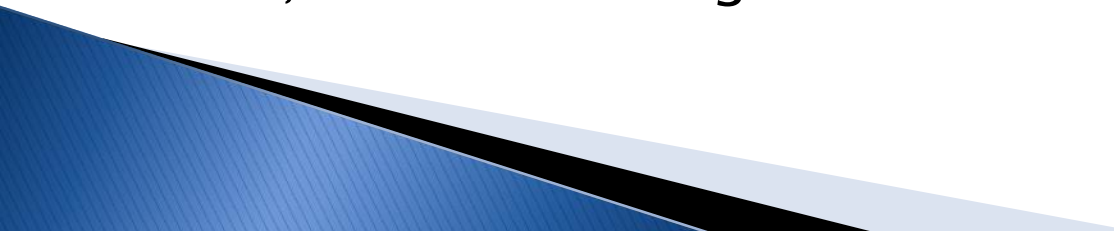
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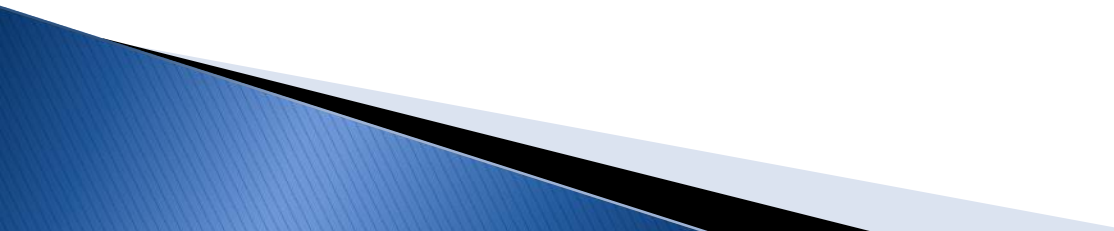
Presentation Overview

1. Chronology of disorders with unexplained symptoms and war
 2. Critical review of CTE, blast and mild TBI
 3. Update on ongoing VA, DoD and Academic Multi-Center, Longitudinal Studies of repetitive mild TBI and blast exposure, including the CENC Longitudinal Study
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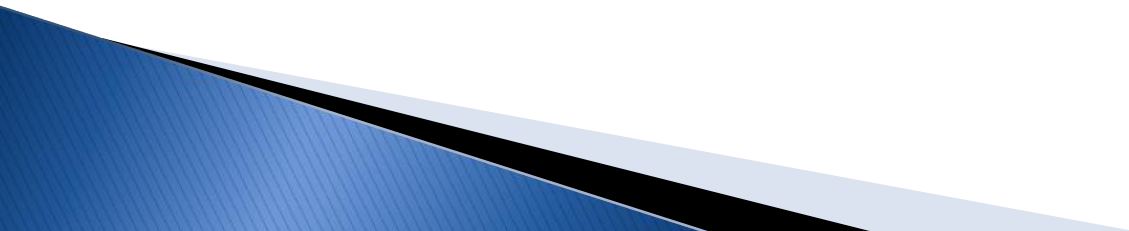
Presentation Overview

4. Evidence-Based Diagnostic Testing for individuals with combat-related exposure to blast and/or repetitive mild TBI who believe they are at risk for or have CTE
 5. Clinical Practice Guideline-directed, comprehensive approach to the clinical management for individuals with combat-related exposure to blast and/or repetitive mild TBI who believe they are at risk for or have CTE
 6. Recommendations on risk communication techniques for Veterans with combat-related exposure to blast and/or repetitive mild TBI who believe they are at risk for or have CTE, and their caregivers and clinicians
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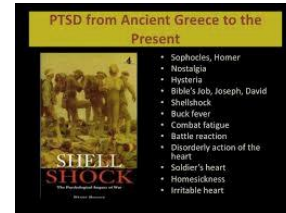
How Did We Get Here?

- ▶ Humans have been sustaining mild TBI's (and experiencing PTSD) for millions of years, and yet we have no significant reports of related long-term effects in any great amount until the last 20 years.
 - ▶ High-contact athletes have been known to develop cognitive-behavioral issues for 100 years.
 - ▶ Combat-exposed Veterans have been known to develop behavioral issues for centuries.
 - ▶ NFL + OEF/OIF + \$\$\$ + Fame = Perfect Storm
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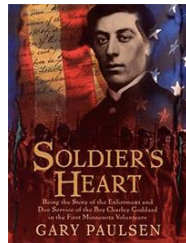
Chronology of disorders with unexplained symptoms and war



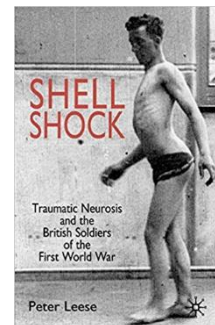
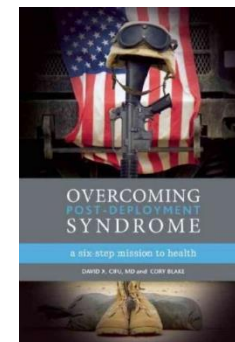
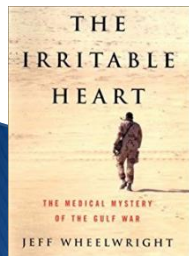
Chronic Multi-Symptom Illness (CMI)



- ▶ The latest name for the disorder associated with military deployment that presents as a combination of medically unexplained chronic symptoms, such as fatigue, headache, joint pain, indigestion, insomnia, dizziness, breathing problems, and memory problems. *McAndrew: JRRD 2016;53(1)*



While environmental (e.g., sand, oil, Agent Orange) and ordinance (e.g., IED, blast) exposures are not uncommon in combat, the association between specific “toxin” and the wide range of symptoms reported is tenuous.



Concussions

Concussion = mTBI



- ▶ **Concussion** (= mild TBI) is a complex pathophysiologic process induced by traumatic forces secondary to direct or indirect impulsive forces to the head that disrupts the function of the brain.
- ▶ Concussion is defined as an alteration or loss of consciousness for up to 30 minutes with associated loss of memory surrounding the event (post-traumatic amnesia) for up to 24 hours.
- ▶ Transient (<24 hours) neurologic sequelae may also be present, including numbness, dizziness, cognitive deficits, discoordination, and alterations in special senses.
- ▶ This disturbance of brain function is typically associated with normal structural neuroimaging findings.



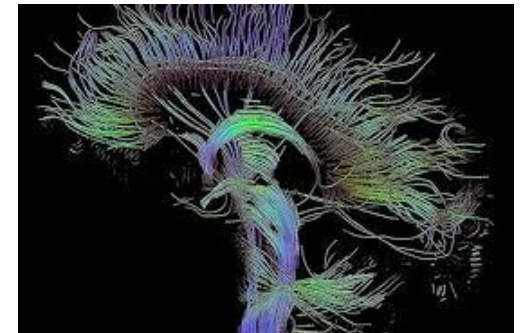
Potentially Concussive Event



- ▶ A PCE is defined as an impulsive force to the head of sufficient intensity that results in acute or chronic symptoms in some individuals, but remain asymptomatic (“subclinical”) in others – no demonstrable neurologic or symptomatic effect.
- ▶ No available diagnostic testing available – new blood biomarker test or BrainScope EEG are of no value.
- ▶ Some have expressed concern about the long-term effects of this potential cumulative trauma disorder.

Challenges to Management

- ▶ Uncertainty of diagnosis
 - Gold standard test is question concerning AOC
 - Imaging (CT Scan) normal >95% of time or high false positive rate (50%) or poor clinical correlations.
 - Few clinicians specialty trained
 - Carpenters like to use wood for everything!
 - Overlap of symptoms with pain, depression, fatigue, stress and life.



Challenges to Management

- ▶ Range of Treatment Options
 - Benign neglect successful >90% of the time
 - Majority of complaints are related to either musculoskeletal or stress-related factors.
 - Army of “specialists” and charlatans
 - Musculoskeletal
 - Vision
 - Vestibular
 - Cognitive
 - Catalogues full of remedies



Persistent Symptoms After Concussion



Post-Concussive Symptoms



- ▶ Acute symptoms resolve in $>85\%$ by 2 weeks
- ▶ As with any mild traumatic injury, patients who are acutely and uniformly treated by experienced clinicians respond rapidly ($>90\%$ musculoskeletal origin), however benign neglect can also get some/many better.
- ▶ Symptoms presenting >2 weeks post-injury are not related to injury

Post-Concussive Symptoms

- ▶ “Post-Concussive Syndrome”
 - Label used if symptoms persist for 3+ months
 - May be seen in 15–30% of concussions and continue for >1 year in 5%.
- ▶ No clear central physiologic reason for symptoms after 2–6 weeks.
 - Axonal disconnection of <5% of white matter tracts
- ▶ ? Chronic pain, anxiety, learned behavior

Common signs of concussion:



Dizziness



Nausea



Headaches



Light
Sensitivity



Confusion

Challenges to Management

- ▶ Individuals bring beliefs, fears and biases
 - Media is replete with concussion and dementia stories
 - Anxiety, misunderstanding, variable compliance, and symptom attribution affect efficacy
 - Differing opinions, prior experiences and outside influences (internet!) affect level of self-efficacy
 - Healthcare system favors testing and illness



Post-Concussive Management – Integrative Medicine

► Education

- Diagnosis – explain multiple contributors
- Prognosis – optimism, self-actualization
- Health Management – Fitness, Sleep, Diet, Mind/Body

► Interventions

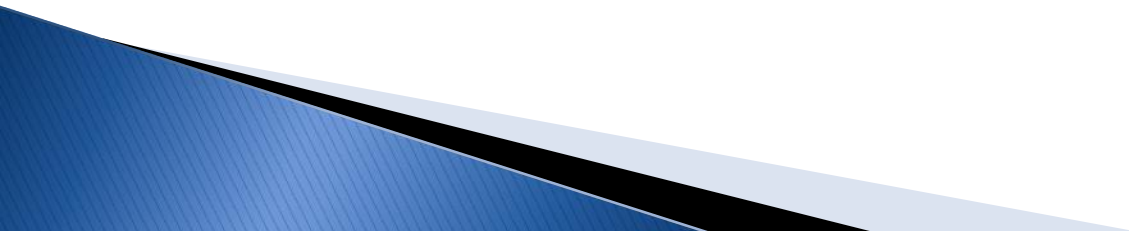
- Sleep – sleep hygiene, medications
- Pain – pain management, non-narcotic medications (short term)
- Behavior – counseling, mood stabilizers (at full dosing)
- Cognition – adaptive strategies, assistive technology
- Fatigue – sleep, fitness, diet, counseling

► Goals

- Normalization
- Deinstitutionalization
- Return to productivity and activity
- Reintegrate into social roles and activities



Blast-Related Concussion



One Explosion/Blast has Multiple Mechanisms of Injury



Wall of Air (Primary)



Blast Wind (Primary)



Flying Debris
(Secondary)

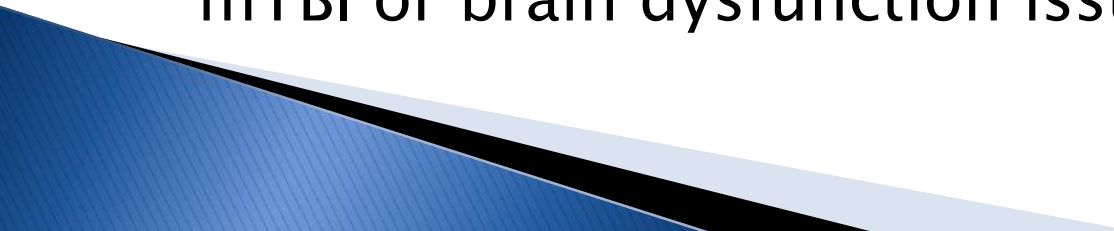


Displacement
(Tertiary)



Collapse Building
(Quaternary)

What is a blast-related mTBI?

- ▶ Per DoD, there have been approximately 10 “pure” blast mTBI from OEF/OIF, but it’s not clear what this even means.
 - ▶ No definitive literature supporting the existence of a blast-related mTBI without physical forces on head.
 - ▶ The head and/or body are moving in >99% of blasts.
 - ▶ Breacher research (munitions experts) that features repeated blast exposure has NOT revealed definitive mTBI or brain dysfunction issues.
- 



Combat Concussions



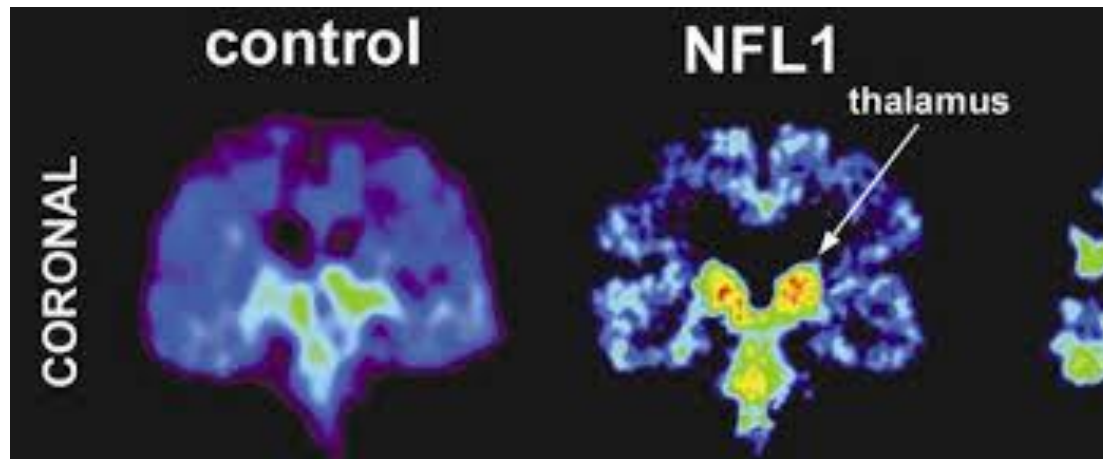
- ▶ 16–20% of OEF–OIF–OND Veterans who received VA medical care have confirmed TBI and 8% were still symptomatic when initiating care at VA
 - ~200,000 total (>1,100,000 screened) in VA
 - 90,000 symptomatic
 - >98% mild
 - <2% moderate–severe
 - >50% due to MVC
- ▶ 75% of Veterans with symptomatic mild TBI also have at least one mental health diagnosis, most commonly Post Traumatic Stress Disorder (PTSD)
- ▶ 90% will have either PTSD or chronic pain disorder



How is blast-related mTBI unique?

- ▶ Definitive research findings identifying the presence of any blast-specific contributions to mTBI without blast forces (i.e., head acceleration-deceleration) is lacking. Similarly, no blast-related PCE research findings!
- ▶ No literature supporting the existence of a blast-related mTBI without physical forces on head.
- ▶ Psychologic stressors of concussion resulting all or in part from a blast exposure must be considered.
- ▶ Unclear if further research is needed?

Chronic Traumatic Encephalopathy



ALZHEIMER'S DISEASE IS THE
6TH LEADING
CAUSE OF
DEATH
IN THE UNITED STATES

MORE THAN
5 MILLION

AMERICANS ARE LIVING WITH ALZHEIMER'S

1 IN 3 SENIORS
DIES WITH ALZHEIMER'S
OR ANOTHER DEMENTIA



IN 2015, MORE
THAN 15 MILLION
CAREGIVERS
PROVIDED AN
ESTIMATED

18.1 BILLION
HOURS OF
UNPAID CARE

ALZHEIMER'S COSTS CAREGIVERS
MORE THAN THEIR TIME

FAMILY CAREGIVERS SPEND MORE THAN
\$5,000 A YEAR
CARING FOR SOMEONE WITH ALZHEIMER'S

FOR SOME FAMILIES THIS MEANS
MISSING A VACATION

BUT FOR OTHERS, IT MAY MEAN
GOING HUNGRY

EVERY
66 SECONDS

SOMEONE IN THE UNITED STATES
DEVELOPS THE DISEASE



IN 2016, ALZHEIMER'S AND OTHER
DEMENTIAS WILL COST THE NATION

\$236 BILLION

IT
KILLS
MORE
THAN

BREAST AND
PROSTATE CANCER
COMBINED



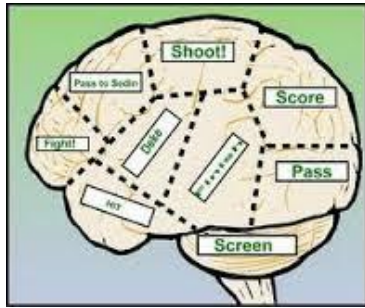


Iraq War combatants (U.S.) with mTBI
report 1–150 mTBIs (~4 average).

NFL players sustain 3,000–8,000
concussions during a lifetime of sports.

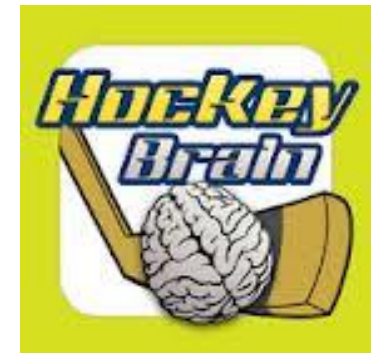
Your speaker has sustained 5–6
concussions in his timid, little life





Q: Do TBI's predispose for late life degeneration?

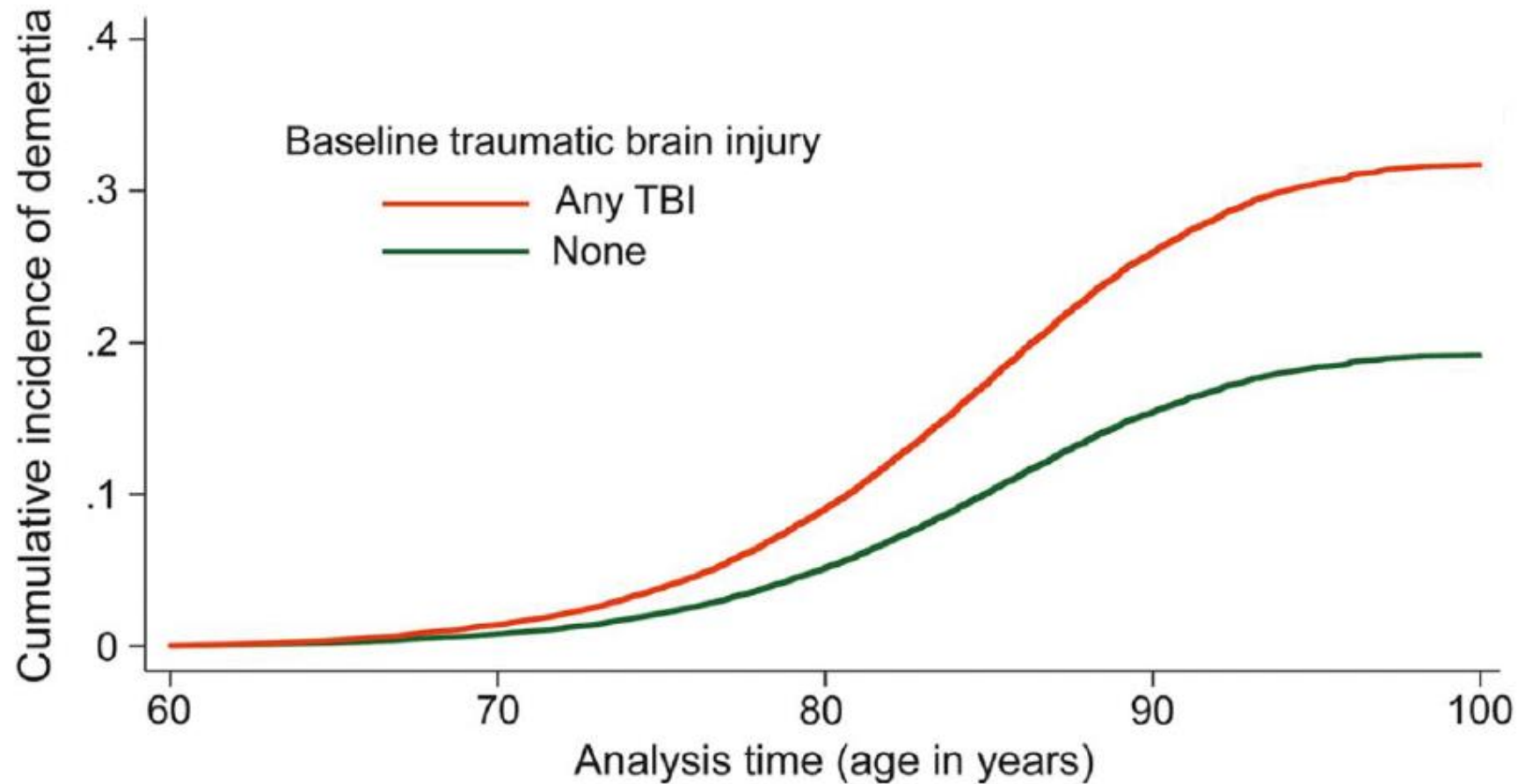
A: Yes



Q: Is someone who has sustained 5–6 mTBI's going to develop CTE?

A: *(Um, what was the question again?)* **NO!!!**

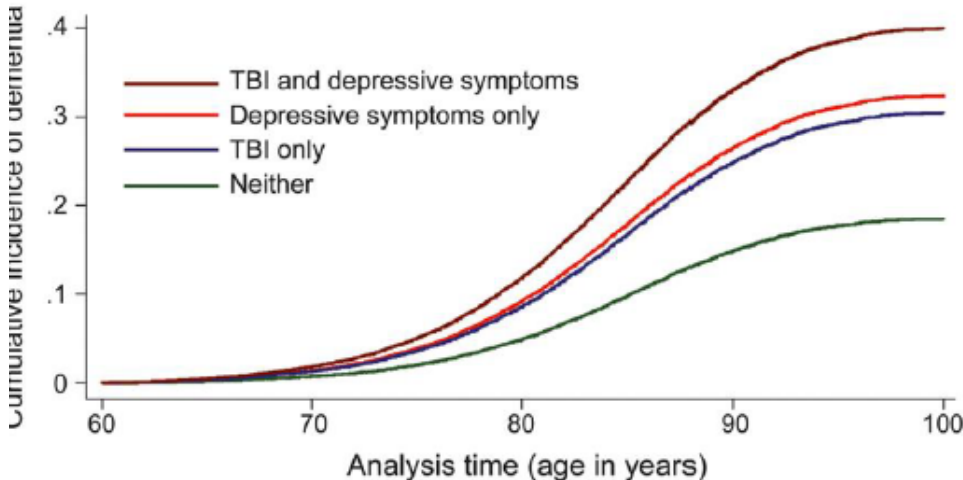
60% Increased Risk of Dementia with TBI



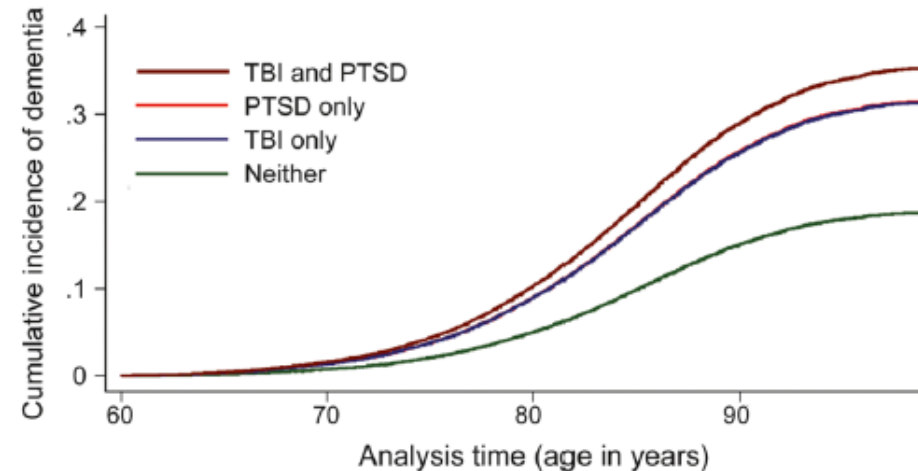
Adjusted HR:1.57; 95% CI (1.35–1.83)

Comorbidities Have an Additive Effect on Dementia Risk

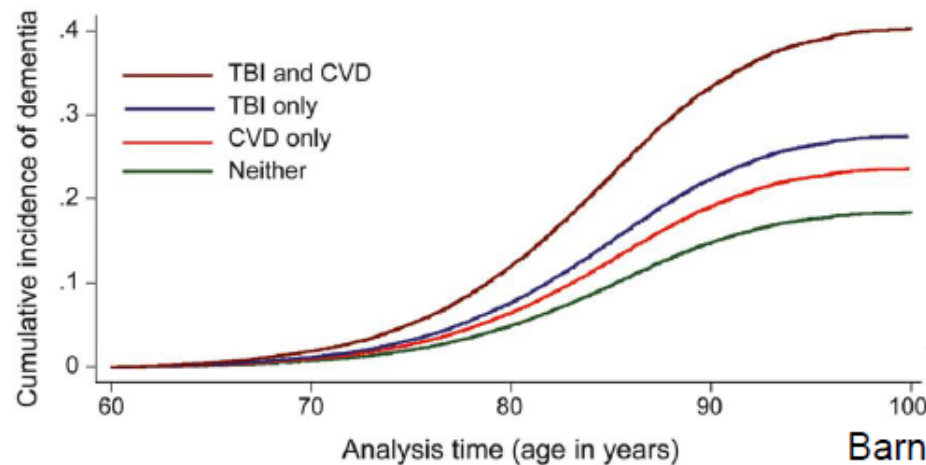
Depression



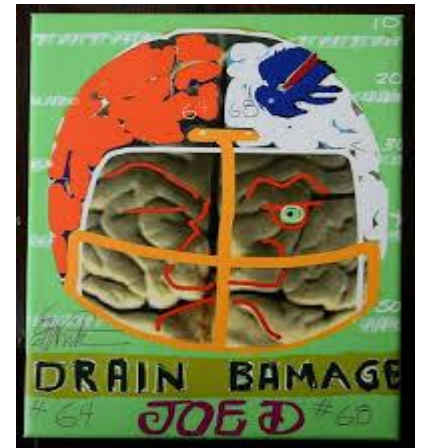
PTSD



Cerebrovascular Disease



Chronic Traumatic Encephalopathy

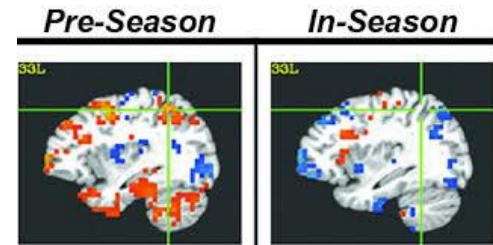


NFL players sustain 3,000-8,000 concussions during a lifetime of sports

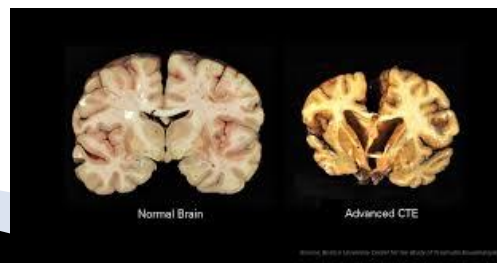
Chronic Traumatic Encephalopathy

- ▶ CTE (Punch Drunk, Dementia Pugilistica) begins insidiously, usually many years (5–20) after the patients have stopped playing sports, with inattention, mood and behavior disturbances, confusion, and memory loss, and progresses over many years (5+) to a stage of full blown dementia and Parkinsonism.
- ▶ The brain, in CTE, shows atrophy, dilatation of the lateral and third ventricles, and thinning of the corpus callosum.
- ▶ Microscopic examination reveals neuronal loss and **tau deposition** in neurons (**neurofibrillary tangles–NFTs**) and in astrocytes. This pathology involves the cerebral cortex (perivascular areas, deep), white matter, deep nuclei, and the brainstem.
- ▶ Beta amyloid deposition in the form of diffuse and less frequently neuritic plaques is seen inconstantly (unlike AD)

McKee CTE Staging




- ▶ Stage I, headaches and issues related to attention and concentration are common
- ▶ Stage II, the symptoms expanded to include depression, explosivity and short-term memory impairment
- ▶ Stage III, reported symptoms include cognitive impairment and problems with executive functions, specifically planning, organization, multitasking and judgment.
- ▶ Stage IV, there was evidence of full-blown dementia (i.e., memory and cognitive impairments severe enough to impact daily living).



Update on ongoing VA, DoD and Academic
Multi-Center, Longitudinal Studies of
repetitive mild TBI and blast exposure,
including the Chronic Effects of NeurTrauma
Consortium (CENC) Longitudinal Study



CENC 1.0

- ▶ CENC multicenter, VA/DoD research collaboration funded in 2013, linking basic, translational, and clinical neuroscience researchers from the VA, military, academia, and the private sector to effectively address the diagnostic and therapeutic ramifications of mTBI and its long-term effects.
 - ▶ The overarching goal is understanding the lifetime impacts of military service, combat-associated concussions and being a Veteran, in particular with respect to the development of mental health disorders, Alzheimer's dementia and related neurodegeneration.
 - ▶ Research linkages between 15 major VA Centers, 12 DoD Military Treatment Facilities/Research Sites, and more than 30 academic research centers in 20 States and the D.C.
- 



Chronic Effects of Neurotrauma Consortium

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

Dwight D. Eisenhower Army Medical Center,
Fort Gordon, GA

Fort Belvoir Community Hospital,
Alexandria, VA

Hunter Holmes McGuire VA, Richmond, VA

James A. Haley Veteran's Hospital, Tampa, FL

Iowa City VA Health Care Center

Medical College of Wisconsin, Milwaukee, WI

Medical University of South Carolina,
Charleston, SC

Michael E. DeBakey VA Medical Center,
Houston, TX

Milwaukee VA Medical Center,
Milwaukee, WI

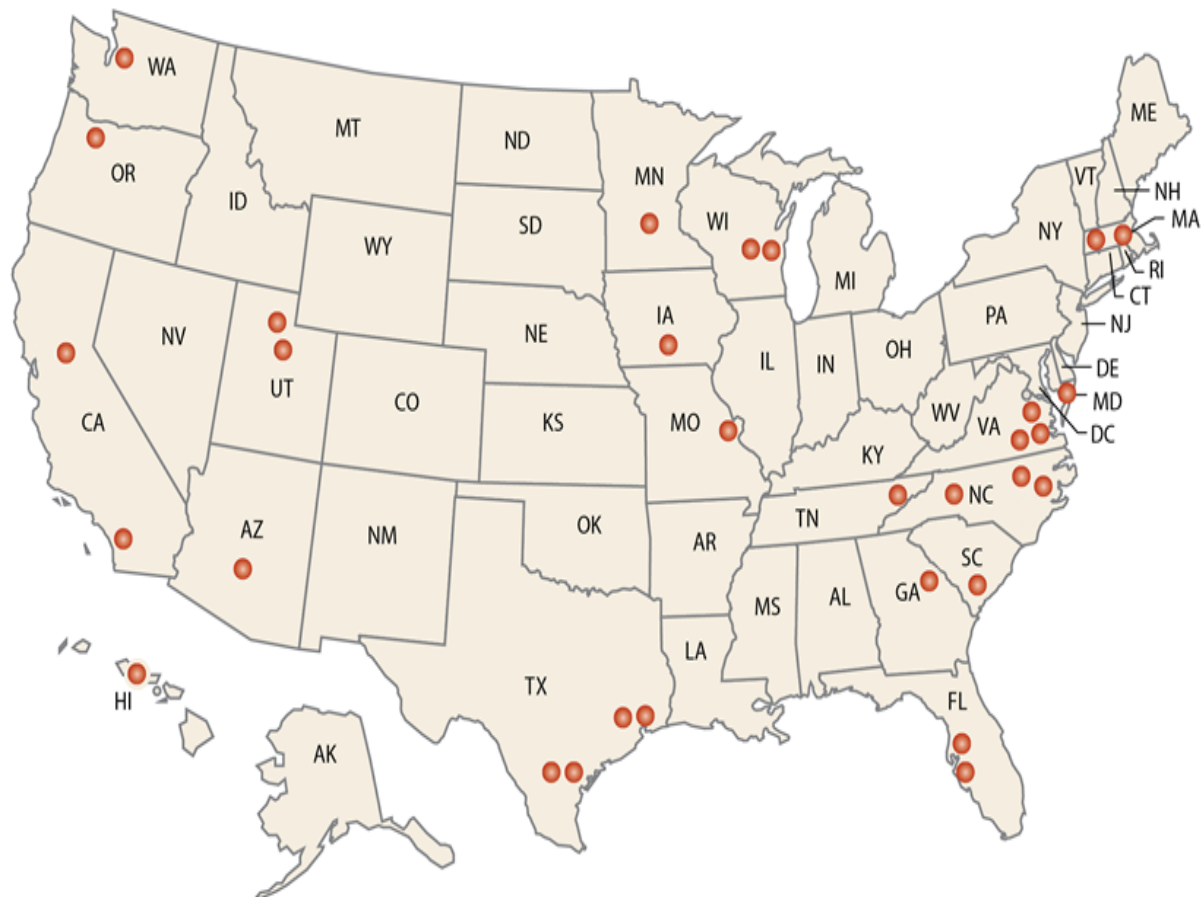
Minneapolis VA Health Care System

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 Hawaii, Manoa, HI

University of Utah, Salt Lake City, UT

University of Washington, Seattle, WA

VA Boston Healthcare System


VA Portland Health Care System

VA San Diego Health Care System,
San Diego, CA

Virginia Commonwealth University,
Richmond, VA

WG Hefner VA Medical Center, Salisbury, NC

CENC Findings

- ▶ More than two-thirds of Servicemembers and Veterans with persistent difficulties after combat concussions and related issues are high functioning, employed and managing well in the community more than 7 years after injury.
 - ▶ One-third are demonstrating ongoing and increasing difficulties that are requiring significant health care utilization.
 - ▶ None of the subjects is exhibiting signs of dementia on average 9 years from last mTBI.
 - ▶ Female subjects have greater symptoms than male.
 - ▶ Servicemembers and Veterans with combat-related concussions and associated conditions (PTSD, pain, depression, substance use, elevated suicide risk) represent a unique and high-risk population.
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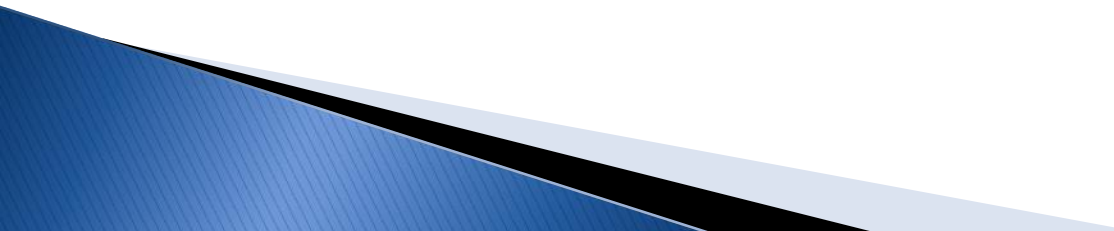
CENC Findings

- ▶ Linkages have been identified between elevated lifetime risks for neuro-degeneration, including Alzheimer's dementia and Parkinson's disease, chronic pain, opioid misuse, and PTSD in Servicemembers and Veterans who have experienced TBI.
- ▶ Multi-modal research assessment techniques have been developed that allow for more accurate diagnoses and clinical characterization. As of yet, these techniques and technologies (e.g. biomarker, imaging, eye-tracking, qEEG) are not appropriate for every day, clinical usage, and the existing diagnostic, assessment and intervention protocols that exist in the VA Polytrauma System of Care are state-of-the-art and clinically appropriate.

CENC Findings

- ▶ While evidence-based, comprehensive clinical services for the care of Servicemembers and Veterans with persistent difficulties due to military service and combat-related concussion exist across VA's Polytrauma System of Care, a number of individuals are not aware and/or accessing these services.
- ▶ While there exist a range of novel techniques and technologies (e.g., hyperbaric oxygen, transcranial magnetic stimulation, neurofacilitation) that are being either advocated or researched for the clinical care of Servicemembers and Veterans with military service and combat-related concussions, none of these newer treatments are yet appropriate for recommended for this population.
- ▶ The comprehensive, symptom-based, team-directed care provided through the VA Polytrauma System is the gold standard.

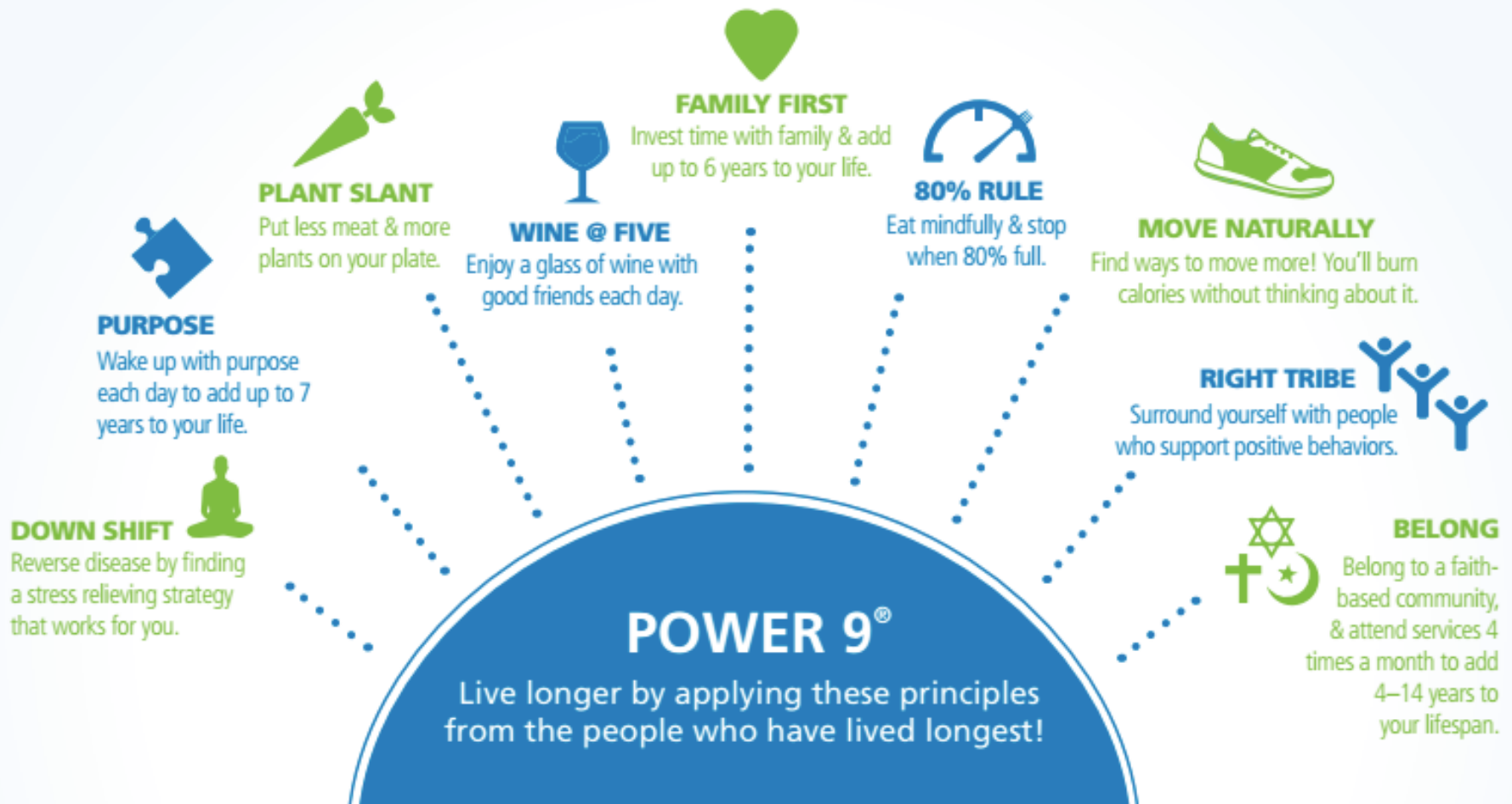
Clinical Practice Guideline–directed,
comprehensive approach to the clinical
management for individuals with
combat–related exposure to blast
and/or repetitive mild TBI who believe
they are at risk for or have CTE.



Dementia-related Factors

- ▶ Nine modifiable lifestyle factors account for up to 50% of all cases of dementia
 - Limited education in early life
 - hearing loss
 - Hypertension
 - Obesity
 - Smoking
 - Depression
 - Physical inactivity
 - Social isolation
 - Diabetes
- ▶ No single risk or protective factor is dominant.

Ashby-Mitchell: Alzheimer Res Ther 2017
Norton: Lancet Neurology 2014



75% of chronic diseases preventable
One-third of dementias preventable

Buettner: The Blue Zone 2008

Dementia-related Factors

- ▶ Repeated TBI's may play a small role (1%) in increasing the risk for dementia.
- ▶ The presence of the apolipoprotein E (APOE) ϵ 4 allele may increase AD risk by 8%.
- ▶ In addition to depression, intermittent or persistent mental illness likely increases risk.
- ▶ Spending enough time getting tests and seeing doctors likely also increase the risk for dementia (? in the doctors)

Diagnosing Dementia

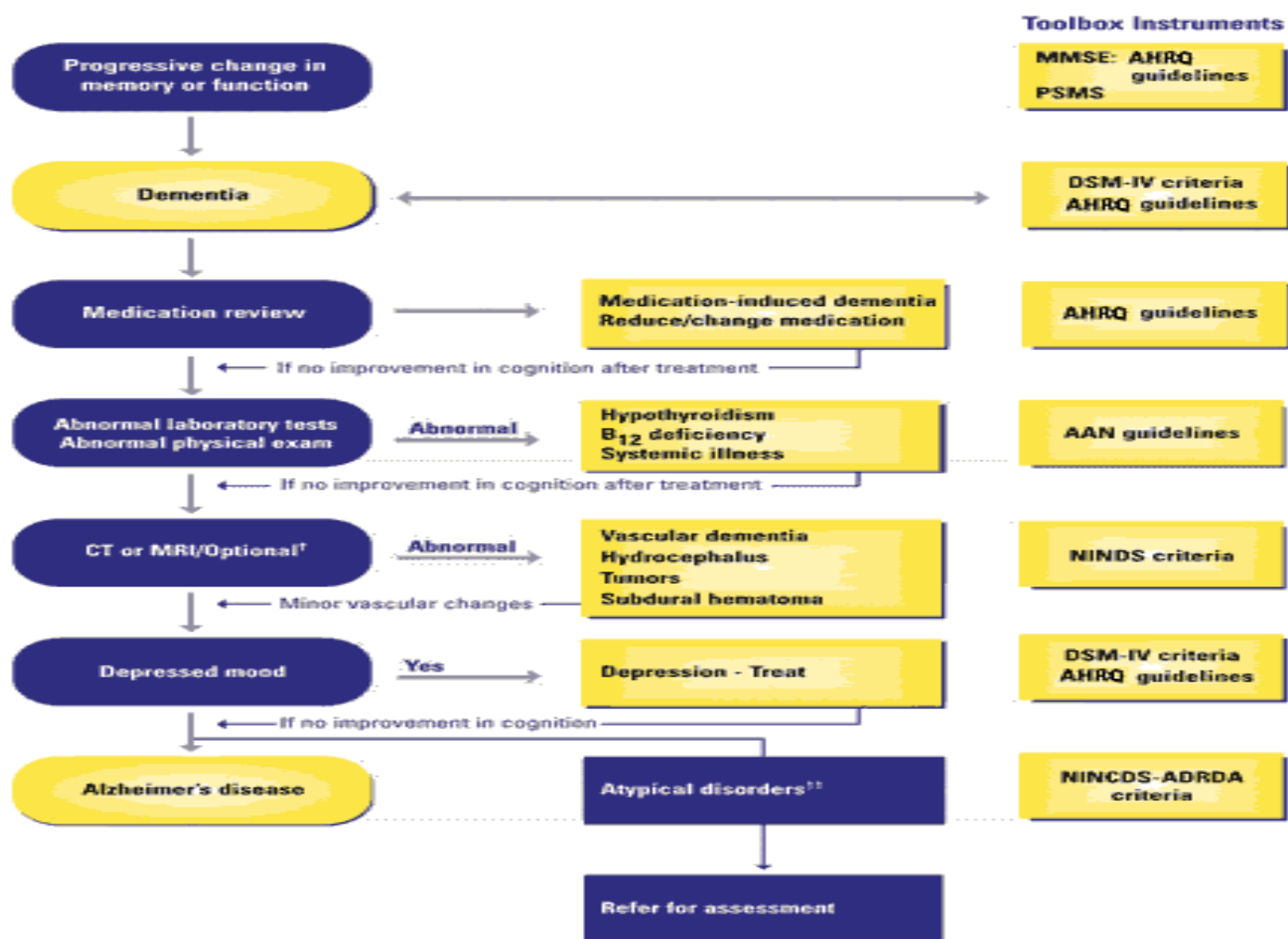
- ▶ The chance you will ever see CTE in your lifetime is about the same as Kuru, Jakob–Creutzfeldt or Cerebral Trichinosis (0%)
- ▶ While unusual, early-onset (Alzheimer's-type) dementia is not uncommon, however it has NOT been associated with concussion.
- ▶ On the other hand, there is extreme value to acknowledging that the individual is having difficulties that
 - warrant an evaluation,
 - can be definitively diagnosed, and
 - have a range of evidence-based treatments

Diagnosing Dementia

- ▶ Progressive disorder resulting in impairment in cognitive function. The clinical symptoms associated include;
 - memory loss
 - language disorders
 - visuospatial impairment
 - behavioral disturbances.

- ▶ NINCDS–ADRDA criteria include:
 - Dementia established by examination and objective testing
 - Deficits in two or more cognitive areas
 - Progressive worsening of memory and other cognitive functions
 - No disturbance in consciousness
 - Onset between ages 40 and 90
 - Absence of systemic disorders or other brain diseases, which could account for the deficits in memory and cognition, should also be established.

Atypical cases of dementia should be referred to specialists for assessment.



* Developed and endorsed by the *TriAD* Advisory Board. ©1996 Pfizer Inc and Eisai Inc., with special thanks to J. L. Cummings. Algorithm reprinted from *TriAD*, Three for the Management of Alzheimer's Disease, with permission.

† It is required in patients with focal signs, rapid progression, and headache.

†† This category will contain rare dementias (e.g., frontotemporal degenerations, Jakob-Creutzfeldt disease, Parkinson's disease [and other movement disorders that present with dementias]) that should be considered when unusual clinical features are present or a rapidly progressive course is noted.

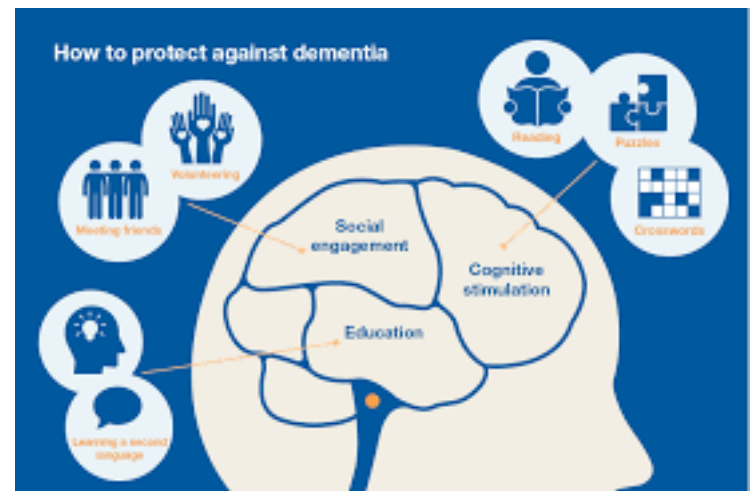
Diagnosing Dementia

- ▶ A patient who presents to a TBI or MH clinic with persistent or worsening cognitive (or behavioral) deficits should be evaluated the same way as any individual;
 - History – Neurologic change, new TBI/trauma, new MH symptoms, SA/EtOH, Medications, Life Stressors, Sleep, Diet, Activity, Work, Metabolic
 - Exam – MMSE, MOCA, Weight, Cardiovascular, Pulmonary, Behavioral, Neurological, Endocrine
 - Function – Activity/Exercise, Leisure Activity
 - Testing – Limited (n.b.: Role of Imaging, NeuroPsychological, EP)
 - Management – If you feel that you have nothing to offer, then reconsider your role!!

Managing “Dementia”



- ▶ Dementia is a 20–60 year prodromal disease
 - We are seeing the effects in the last 5 years of life
 - We are attempting to intervene in the last 2 years of life
- ▶ Even though 99% of the folks we see will NOT have classic dementia, they all likely have elevated risks.
- ▶ And we wonder why we are failing??



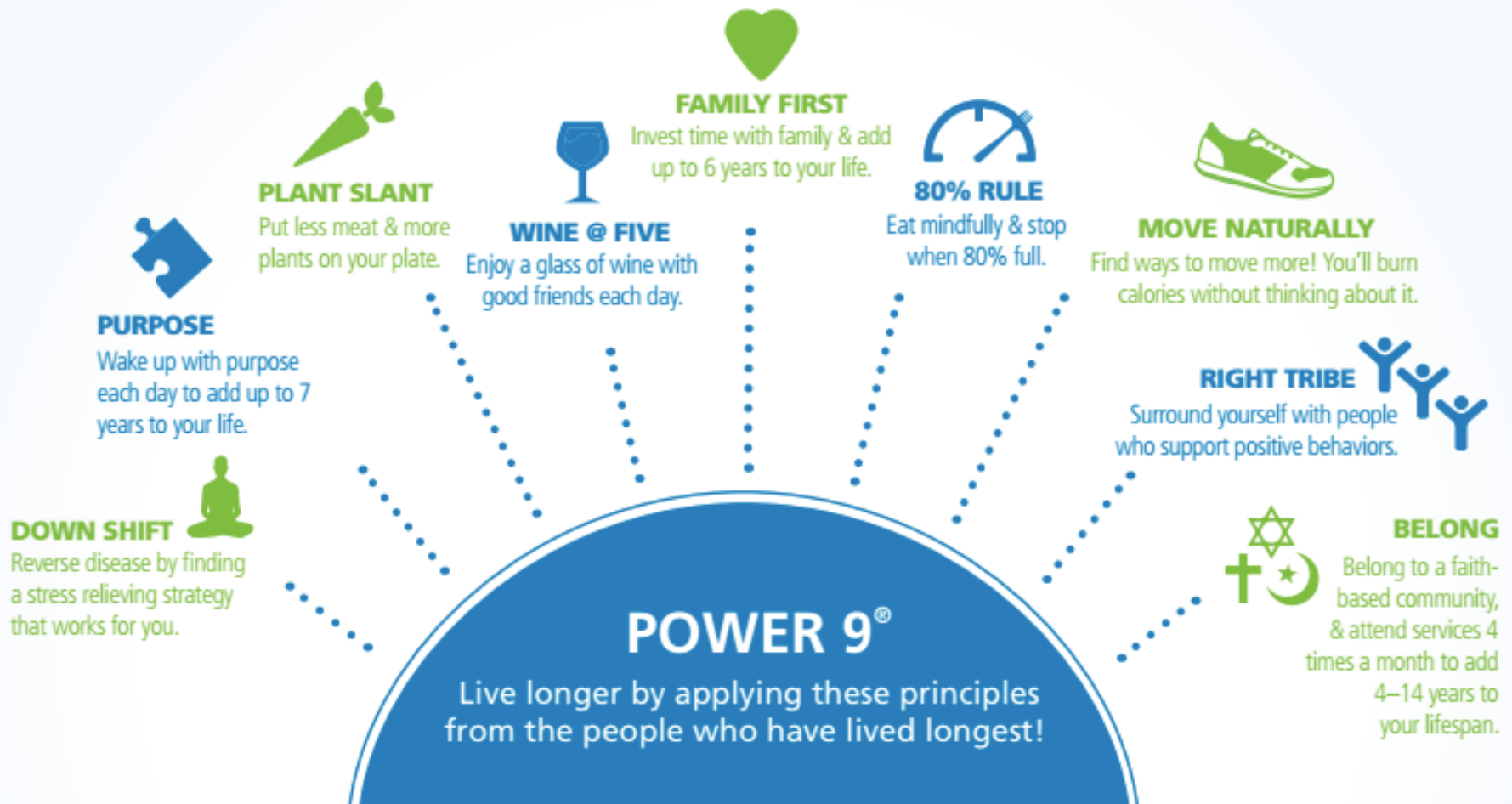
Using the Rehab Model to “Treat” Dementia

- ▶ Research efforts in dementias focus on
 - preventative strategies for dementia risk factors
 - pharmaceutical interventions to slow progression
- ▶ Rehabilitation strategies have demonstrated similar/better efficacy than medications for prevention or treatment
 - symptom management
 - lifestyle modifications
 - physical exercise
 - cognitive exercise
 - formal rehabilitation therapy

Implementing Brain Health

- ▶ FINGER study:
 - Double-blind, randomized clinical trial of 1260 individuals 60–77 years with normal cognition for age and a high risk of dementia
 - Assignment to a 2-year multidomain intervention (diet, exercise, cognitive training, social stimulation, and management of vascular and metabolic risk factors)
- ▶ Interventions are feasible and safe
- ▶ Interventions associated with significant beneficial effect on overall cognition, executive functioning, and processing speed, as well as body mass index, dietary habits, and physical activity.

Ngandu: Lancet 2015



75% of chronic diseases and one-third of dementias preventable

**Diet, Exercise, Sleep, Stress Management, Pain Care,
Productivity, Social Integration, Family, Faith-Based Community**

Using the Rehab Model to “Treat” Dementia

- ▶ First, do the obvious
 - ▶ Reassure the individual and family
 - ▶ Treat medical and psychological issues
 - ▶ Optimize medication regimes
 - ▶ Identify “symptom specific” approaches
 - ▶ Establish a therapeutic alliance

Wheel Of Health



Self Care

Professional Care

Duke Integrative Medicine

© Copyright 2010 Duke Integrative Medicine/Duke University Medical Center

- ▶ Second, do the hard part
 - ▶ Identify short- and long-term cognitive wellness and brain health goals
 - ▶ Create a path to engagement (IM, MI, MIMI?)

Physical Exercise and Dementia

- ▶ Meta-analysis (1970–2003) to determine whether physical exercises are beneficial for people with dementia and related cognitive impairments.
- ▶ Studies were limited to randomized trials evaluating exercise in persons 65 years of age or older with cognitive impairment. Studies included quantitative results for physical fitness, physical functioning, cognition, or behavior outcomes.
- ▶ A total of 2020 subjects participated in the 30 trials that met the inclusion criteria. Significant summary effect sizes (ES) were found for strength, physical fitness functional performance, cognitive performance and behavior. The overall mean ES between exercise and non-exercise groups for all outcomes was 0.62.
- ▶ **Conclusion: Exercise training increases fitness, physical function, cognitive function, and positive behavior in people with dementia and related cognitive impairments.**

Heyn :The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil 2004;85:1694-704.

Physical Fitness and Dementia

- ▶ Critical review of literature from 2006–2010 on role of physical fitness on health.
- ▶ Apart from not smoking, being physically active is the most powerful lifestyle choice any individual can make to improve their health.
- ▶ Individuals have an element of control over some of these factors, including obesity, diet, smoking and physical activity.
- ▶ Regular moderate to intense physical activity is associated with decreased risk of coronary heart disease, ischemic and hemorrhagic stroke, cancers (and exercise can enhance cancer recovery), osteoporosis, type 2 diabetes, depression, obesity and high blood pressure.
- ▶ There is growing evidence that physical activity could decrease the risk of dementia in the elderly.

Alford: Intl J Clin Pract 2010;64(13):1731–1734

Cognitive Fitness and Dementia

- ▶ The literature supports maintaining general cognitive fitness in dementia, especially when combined with acetylcholinesterase inhibitors
 - slow the rate of cognitive decline
 - slow the rate of functional decline
 - decrease negative emotional
- ▶ Cognitive fitness may be maintained via
 - Leisure skills training and activities
 - Individual training
 - Group training and Day Care
 - Internet-based training

Recommendations on risk communication techniques for Veterans with combat-related exposure to blast and/or repetitive mild TBI who believe they are at risk for or have CTE, and their caregivers and clinicians

Counseling on TBI and CTE

- ▶ Acknowledge their issues and concerns.
- ▶ Don't over explain or hedge your answer.
- ▶ The risk of developing dementia from a single concussion is zero. The risk of developing dementia from 10 concussions is just barely above zero.
- ▶ Undertreated symptoms (post-concussion, mental health, pain) may be a more relevant risk factor for dementia.
- ▶ Lifestyle factors, general wellness, and integration into society are biggest risk factors

