TBI – Neuropsychiatric Sequelae

Chair: Lori Davis, MD; Tuscaloosa VA and University of Alabama at Birmingham

Members:
Thomas Novack, PhD; UAB Traumatic Brain Injury Model System (UAB-TBIMS)
Benjamin Hill, PhD; University of South Alabama
Alice Theadom, PhD; National Institute for Stroke and Applied Neurosciences, Auckland University of Technology, New Zealand (BIONIC)
Murray Stein, MD; University of California San Diego; DoD INjury and TRaumatic STress (INTRuST) Consortium
David Williamson, PhD; Janssen Scientific Affairs
Brendon Binneman, MD; Pfizer
Maria Bergman, PhD; Tuscaloosa VA Medical Center

Shell Shock

- World War I signature injury due to blast force
- "Shell shock" first appeared in 1915 *Lancet* of British soldiers exposed to blast events c/o insomnia, reduced visual field, loss of taste, hearing, memory.
- As the war continued, the condition was attributed to weakness of nerves
- Reduced research toward blast-force injury as physical until 1951 after WWII US Atomic Energy Commission Blast Biology Program

Overview of Clinical Issues of Concern when Designing Trial

- Localization and mechanism of injury to brain
- Severity of brain injury
- Number of lifetime brain injuries
- Age and time since brain injury
- Pre-injury cognitive and psychosocial functioning
- Psychosocial Issues (e.g. financial resources, transportation/housing, and social supports)
- Premorbid psychiatric conditions
- Characteristics of neuropsychological sequelae
    - Postconcussion syndrome
    - Depression and mood disorders
    - Post-traumatic stress disorder
    - Agitation, aggression
    - Impulsivity; behavioral dysregulation
    - Impaired self-awareness
    - Suicidality

ASENT
American Society for Experimental NeuroTherapeutics, Inc.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Recruitment Issues

- Timeframe since injury (i.e. 24 hours, weeks, etc)
- TBI common, but the specific eligibility criteria narrow the population to the point of rare cases
- Population reluctant to seek treatment, stigma
- Population suspicious of research, guarded
- Concomitant medications or treatments
- Participation burden is high and requires effort
- Inconvenient to come to appointments when trying to get back to their daily work and routine

Adherence and Attrition

- Much higher in mild TBI cohorts
- Relates to participation burden
- Relates to returning to work and life activities
- In-home computer testing may reduce attrition but environment is not controlled
- Memory problems impacts adherence
- Prioritize assessments (order of administration)
- Subjects are PARTICIPANTS, engagement

Treatment Considerations

- One-drug, One-outcome model is failing
- Behavioral interventions should be included
- Person-centered treatment approaches
- Within subject design vs. population based
- Course of treatment variable
- Monitor recurrent TBI during the trial
- Monitor drug-alcohol use during the trial
- Monitor suicidality during the trial

Outcome Measurements

- Performance validity and effort testing
- Reliability of instruments in TBI population
- Specific single outcome may be too narrow
- Matrix of outcomes (concerns of multiplicity)
- Person-centered outcomes
- Functional outcomes and returning to work
- Quantitative and Qualitative Outcomes

TBI Clinical Trials

- Buspirone for TBI Irritability and Aggression
- VNS to Augment Recovery
- Vestibular Rehabilitation and Balance Training After TBI
- Early Propranolol After TBI: Phase II
- Stem Cell Therapy in TBI
- Xbox in the Rehabilitation of Chronic TBI
- Light Therapy for Moderate TBI
- Virtual Reality (VR) Treatment for Balance Problems in TBI)
- Lactate Therapy After TBI
- Anger Self-Management in TBI
- Brain Stimulation for Mild TBI
- Influence of Cognitive Rest on Minor TBI

Actionable Recommendations

- Recognize the neuropsychiatric problems as having a biological, psychological, and behavioral etiology
- Establish consistent minimal data set
- Data repositories
- Include analysis for validity and effort as inclusion criteria or moderator of outcomes
- Noninvasive monitoring and detection devices
- Suicide risk monitoring
- Recovery oriented rehabilitation to manage “the new normal”
- Supported employment to return to work