Neurobehavioral Function in Adults Recovering Consciousness after Severe Traumatic Brain Injury: A Scoping Review

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Study Aims
- This scoping review aims to report the findings of current literature examining the assessment of neurobehavioral function and recovery along the continuum of disorders of consciousness (DOC) from coma to full consciousness.
- This study is designed to capture the range of constructs researchers have used to measure NBF during recovery of consciousness.
- The research question for this review was: “What constructs are most frequently used to assess neurobehavioral function in adults recovering consciousness after severe TBI?”

Analytic Framework
- A scoping review examines the extent and nature of the research, identifies gaps in the literature, and may establish the significance of commencing a full systematic review (Lavac, Cleallouin, & O'Brien, 2010).

Background
- Approximately 10% of the 1.7 million traumatic brain injuries (TBI) that occur each year in the US are considered severe and result in significant disability (CDC, 2016).
- As of 2015, there is no approved drug or device to treat TBI.
- A challenge in demonstrating the effectiveness of drugs and devices to treat TBI is the lack of sufficiently precise outcome assessments that are approved as federally qualified endpoints.
- The Glasgow Coma Scale (GCS) and Glasgow Outcomes Scale (GOS) are the most commonly-used measures of neurobehavioral function (NBF) in TBI clinical trials.
- Clinical Outcome Assessments (COAs) are “reported” assessments influenced by human choices, judgments, or motivation and may provide direct insight to benefit.
- Four types of COAs:
  - Patient reported outcome (PRO)
  - Clinician-reported outcome (ClinRO) measures
  - Observer-reported outcome (ObsRO) measure
  - Performance outcome (PerfO) measures
- FDA Federally Qualified Endpoint Measures: Roadmap to patient-focused outcome measurement includes:
  - Understanding the disease
  - Conceptualizing treatment benefit
  - Selecting/Developing outcome measures

Methods
- Two databases, Scopus and PubMed, were searched using 21 search terms generated from three main concepts: “traumatic brain injury” (n=3), “neurobehavioral function” (n=16), and “outcomes” (n=12).
- Study inclusion criteria:
  - Published within the past 5 years
  - Involving adult humans (≥18 years old)
  - Relevant to severe TBI
- Relevant to DOC:
  - The initial search identified 229 articles were identified. After the removal of duplicates, 211 articles were retained and reviewed for inclusion.
  - 58 met the inclusion criteria. These articles were grouped thematically based on content related to assessment of NBF and recovery of consciousness.
- Four themes were identified: “Predicting Outcomes”, “Non-Pharmacological Treatment”, “Pharmacotherapy”, and “Neural Pathways”.
- Clinical Outcomes were identified within each article and grouped as outcomes related to “clinical outcome assessments”, biometrics and biomarkers, “neuroimaging and neurophysiology”, and “other”.

Most Commonly Identified Outcome Measures Were Clinical Outcome Assessments
- 162 incidences of COAs were reported in 58 articles
  - The majority of incidences of COAs were ClinROs (n=115)
  - The most frequently reported ClinROs were:
    - Glasgow Coma Scale: 29 articles
    - Coma Recovery Scale-Revised: 21 articles
    - Glasgow Outcome Scale or GOS: 17 articles
  - 50 different COAs were identified
  - No ObsROs or PerfROs were found in any of the articles

Most Commonly Occurring Themes Were Predicting Outcomes and Non-Pharmacological Treatment
- Most common constructs included:
  - Role of genotypes & biomarkers
  - Neuro-imaging and neurophysiology
  - Observed behaviors in response to sensory input (e.g. head turning and visual fixation)

Results
- The Glasgow Coma Scale (GCS) and Glasgow Outcomes Scale (GOS) are relatively blunt measures of neurobehavioral function (NBF) in TBI clinical trials.
- Clinical Outcome Assessments (COAs) are “reported” assessments influenced by human choices, judgments, or motivation and may provide direct insight to benefit.
- Four types of COAs:
  - Patient reported outcome (PRO)
  - Clinician-reported outcome (ClinRO) measures
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Prediciting Outcomes
- Most common constructs included:
  - Role of genotypes & biomarkers
  - Neuro-imaging and neurophysiology
  - Observed behaviors in response to sensory input (e.g. head turning and visual fixation)

Non-Pharmacological Treatment
- Most common constructs included:
  - Electrical stimulation
  -coma stimulation
  - Hypoesthesia
  - Familiar voice auditory stimulation, and
  - Interdisciplinary care models.

Neural Pathways
- Most common constructs included relationship between “neural pathways” and recovery of consciousness.
- Auditory network more functionally connected in patients in a minimally conscious state
- Goal directed activity may be initiated due to inability to coordinate precuneus fiber tracts

Pharmacotherapy
- Agents most often reported on included:
  - Amantadine
  - Progesterone
  - Baclofen

Pharmacotherapy Articles Most Often Reported on
- Amantadine, Progesterone, and Baclofen
- 90-day mortality, number of medical complications, discharge disposition
- Most Frequently Reported Clinical Outcome Assessments Were Clinician-Reported Outcomes

Current Literature Focuses on Predicting Outcomes
- The most frequently occurring theme was Predicting Outcomes, followed by Non-Pharmacological Treatment.
- Studies primarily focused on predicting outcomes of patients with TBI. There were many fewer studies describing effective treatments for these patients.
- The focus on predicting outcomes appears to be off target when current classification of TBI severity and type is blunt and treatments for severe TBI are limited.

Diversity of Outcome Measures Dilutes Evidence Base
- This study found a remarkable range in the diversity of reported COAs, biomarkers, neuroimaging and neurophysiology techniques.
- This creates challenges in comparing results across studies and consequently limits the translation of knowledge into practice.
- 50 different COAs were identified but only 3 were reported in more than 5% of the articles (GCS, GOS/GOS, CRS/CRS).
- The GOS and GOS are relatively blunt measures of NBF recovery and the CRS-R has no published sensitivity to change indices.

Connecting Mechanisms of Recovery to Treatment and Outcomes Measurement
- Only a few articles were found related to “neural pathways”
- Understanding the mechanisms of pathology in brain injury and neuroplasticity will likely play a critical role in more precise diagnosis and more targeted treatment for these patients.
- There appears to be a gap in the literature regarding precision in severe TBI diagnoses and linking this to brain pathology in order to design more appropriate and effective treatments.

Future Directions
- This study identified a wide range of COAs measuring NBF.
- The extent to which these assessments address the same content domain and if some domains are poorly addressed remains unknown.
- Treatments for patients with severe TBI could be developed in parallel with studies aimed at better understanding the brain’s pathways and response to TBI.

Limitations
- Search timeframe was limited to studies within the last 5 years.
- Articles in the scoping review are not read to analyze bias or the quality of the study.
- Breadth of the articles is wide rather than deep.

Funding Source
- Study funded by the Joint Warfighter Medical Research Program Grant RW81.XWH.16-2-0023. PI: Pape

References
- TBI Initiative: https://tbiendpoints.ucsf.edu/
- Understanding the Brain's Pathways and Response to TBI: https://www.betterhelp.com/traumatic-brain-injury/