Recovery after moderate to severe TBI and factors influencing functional outcome: What you need to know

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ABSTRACT: Traumatic brain injury (TBI) represents a major cause of death and disability, significantly impacting the lives of 2.5 million people annually in the United States. Long-term natural history studies have clarified that functional recovery continues for up to a decade, even among those who sustain severe TBI. Despite these findings, nihilistic attitudes regarding prognosis persist among clinicians, highlighting the need for improved understanding of the natural history of recovery from TBI and the factors that influence outcome. Recent advances in neuroimaging technologies and blood-based biomarkers are shedding new light on injury detection, severity classification and the physiologic mechanisms underlying recovery and decline postinjury. Rehabilitation is an essential component of clinical management after moderate to severe TBI and can favorably influence mortality and functional outcome. However, systemic barriers, including healthcare policy, insurance coverage and social determinants of health often limit access to inpatient rehabilitation services. Posttraumatic amnesia and confusion contribute to morbidity after TBI; however, early initiation and sustained provision of rehabilitation interventions optimize long-term outcome. Evidence-based reviews have clearly shown that cognitive rehabilitation strategies can effectively restore or compensate for the cognitive sequelae of TBI when used according to existing practice guidelines. Neurostimulant agents are commonly employed off-label to enhance functional recovery, however, only amantadine hydrochloride has convincingly demonstrated effectiveness when used under tested parameters. Noninvasive brain stimulation procedures, including transcranial direct current stimulation and transcranial magnetic stimulation, have emerged as promising treatments in view of their ability to modulate aberrant neuronal activity and augment adaptive neuroplasticity, but assessment of safety and effectiveness during the acute period has been limited. Understanding the natural history of recovery from TBI and the effectiveness of available therapeutic interventions is essential to ensuring appropriate clinical management of this complex population. (*J Trauma Acute Care Surg.* 2024;97: 343–355. Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Traumatic brain injury; disorders of consciousness; biomarkers; outcome; rehabilitation.

NATURAL HISTORY OF RECOVERY FROM MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is projected to remain among the top three contributors to disability and injury-related death until 2030.[1] Current estimates suggest that TBI affects approximately 50 to 60 million individuals globally each year, with a prevalence rate of 787 per 100,000 persons in the United States.[2] However, these figures may not fully capture the true incidence and prevalence of TBI, underestimating its impact. The substantial public health burden of TBI is underscored by its significant economic implications, with an estimated annual cost to the global economy of approximately $400 billion.[1,3] It is imperative to understand the natural history of recovery from TBI and available treatment options for management of this complex condition.

This review focuses on patients who sustain moderate to severe TBI (msTBI). Diagnostic criteria for msTBI typically require one or more of the following symptoms[4]: loss of consciousness (LOC) for 30 or more minutes; posttraumatic amnesia (PTA) for 24 or more hours, or a score <13 on the Glasgow Coma Scale (GCS).[5] Other inclusion criteria may include disorientation and confusion, positive neuroimaging (e.g., hematoma, contusion, penetrating injury, hemorrhage, brain stem injury), seizure, or other neurocognitive deficits.[4,6] It should be noted that patients who meet the clinical criteria for mild TBI but also have an abnormal CT scan are classified as having moderate TBI by the Department of Defense.[7] Severe TBI is frequently associated with transient or prolonged alteration in consciousness. Current practice guidelines recognize four major disorders of consciousness (DoC): coma,[8] vegetative state[9] or unresponsive wakefulness syndrome[10] (VS/UWS), minimally conscious state (MCS),[11] which can be further delineated to MCS plus (MCS+) or MCS minus (MCS−) based on the presence or absence of language,[12] and posttraumatic confusional state (PTCS)[13] (Fig. 1). Incidence and prevalence rates are difficult to accurately estimate in view of high rates of misdiagnosis,[14,15] premature withdrawal of life-sustaining treatment or therapy (WLST),[16] and lack of systematic surveillance.[17]

A prevalent misconception among many healthcare providers is that disturbance in consciousness that persists across the intensive care unit (ICU) stay invariably leads to poor outcome. This false belief can negatively influence early decision making leading to overestimation of poor prognosis and premature WLST. Converging evidence suggests that approximately 70% of deaths that occur in the ICU after TBI are attributable to WLST,[14] underscoring the need for accurate diagnosis and evidence-informed decision-making.

Recovery of Consciousness

Disorders of consciousness are defined by disturbances in arousal and awareness of self or environment. While the neurobiological mechanisms that underpin conscious awareness remain inadequately understood, disturbance in consciousness is most often caused by destructive or compressive bi-hemispheric injury to the cortex and underlying white matter, focal injury to subcortical structures that mediate arousal, and lesions that disconnect cortical, diencephalic, and brain stem pathways.[18] Analysis of data derived from resting state functional connectivity MRI suggests that a brain stem network comprised of the ventral anterior insula, pregenual anterior cingulate cortex and the left rostral pontine tegmentum may play a critical role in mediating consciousness as disconnection within this circuit is consistently associated with coma.[19]

Recent natural history studies have demonstrated the potential for recovery of consciousness well after discharge from the ICU.[20,21] It has also become clear that most patients who survive the acute phase eventually regain consciousness.[21–23] Longitudinal research conducted by the 16-site Traumatic Brain

Submitted: February 19, 2024, Accepted: February 23, 2024, Published online: March 5, 2024.

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DOI: 10.1097/TA.0000000000004305

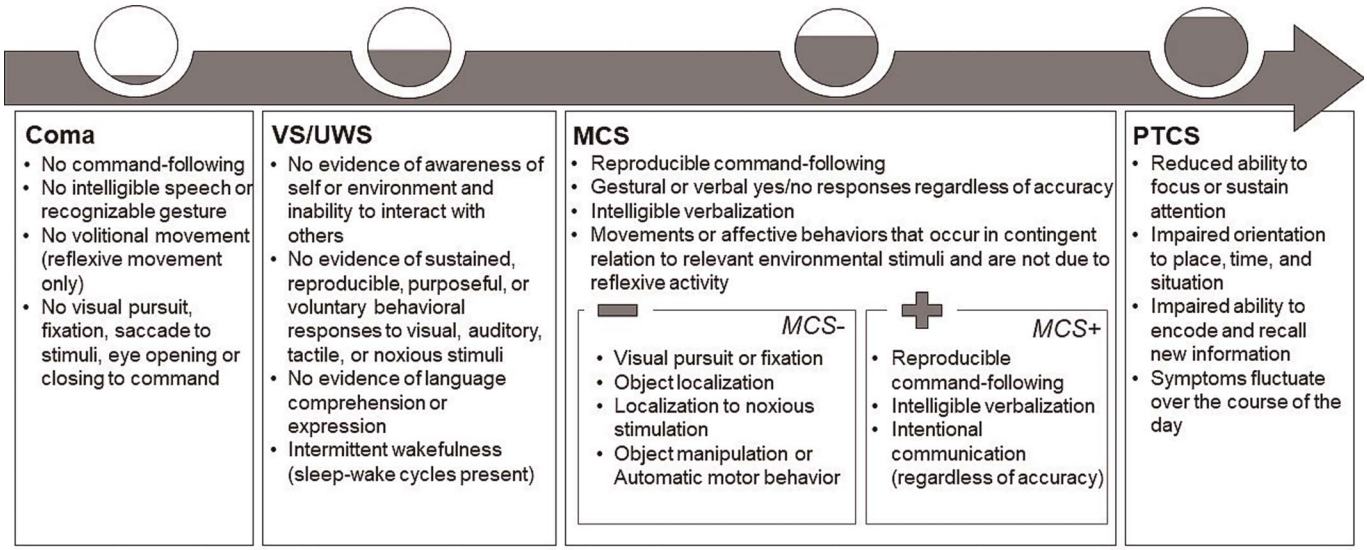

Figure 1. American Academy of Neurology-American Congress of Rehabilitation Medicine-National Institute on Disability Independent Living and Rehabilitation Research diagnostic criteria for coma, vegetative state/unresponsive wakefulness syndrome, minimally conscious state, minimally conscious state-plus, minimally conscious state-minus and posttraumatic confusional state.

Injury Model System (TBIMS) Program (https://www.tbindsc.org/) found that approximately two-thirds of patients followed (n = 386) recovered command-following ability and one-fourth regained orientation during inpatient rehabilitation.[22] Of those who failed to recover command-following while undergoing inpatient rehabilitation (n = 108), more than half did so by 1 year, two-thirds by 2 years, and three-quarters by 5 years.[23] In a follow-up TBIMS study that tracked recovery of consciousness among 7,567 patients evaluated in the emergency department, 57% were not following commands on initial examination, however, the proportion dropped to 12% on admission to inpatient rehabilitation and only 2% by rehabilitation discharge.[23] Notably, patients who were not following commands on rehabilitation admission experienced greater absolute improvement during the rehabilitation course than those with command following.

A cross-sectional study of 362 patients with severe TBI enrolled in the 18-site Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) network (https://tracktbinet.ucsf.edu/) monitored recovery of consciousness in 79 patients who were in VS/UWS at 2 weeks postinjury.[21] Among the 78% who survived to the 12-month follow-up, 84% recovered consciousness by 3 months, 94% by 6 months and 99% by 12 months. Of those with available data who survived to 12 months (n = 56), 25% also regained orientation.[21] In one of the few natural history studies that monitored long-term outcome among patients in nontraumatic VS/UWS who survived beyond 6 months, 21% of the anoxic subgroup and 6% with hemorrhagic stroke recovered consciousness between 6 and 28 months (no significant difference by etiology).[24] Taken together, these findings sound a cautionary note concerning the heavy reliance on recovery of command-following during the acute period as a predictor of subsequent recovery. This tendency may lead to overestimation of poor recovery potential and premature recommendation for WLST. Prior studies have demonstrated that clinicians' subjective judgment of the potential for neurologic recovery is the primary driver in the decision to recommend WLST.[14,15]

Recovery of Behavior

Detecting the transition from an unconscious to conscious state relies heavily on behavioral findings obtained on bedside examination and is used to inform prognosis after msTBI. This is problematic given that behavioral recovery is characteristically slow in the trauma setting and there is little evidence concerning the frequency and time course to recovery of behaviors associated with subsequent functional recovery. Among a cohort of 79 patients who transitioned from coma or VS/UWS to MCS or emergence from MCS, visual pursuit was the most commonly observed initial behavioral sign of recovery of consciousness, followed by reproducible movement to command and automatic movement.[25] In addition, the median length of time to recovery of consciousness was 44 days postinjury.[25]

A second study involving 95 patients who were either in MCS or VS on admission to inpatient rehabilitation monitored reemergence of six target behaviors (i.e., consistent command-following, object recognition, functional object use, intelligible speech, reliable yes-no communication, sustained attention) drawn from the Coma Recovery Scale-Revised (CRS-R) over a 6-week observation period.[26] Behaviors associated with preserved language function (e.g., command-following, intelligible verbalization, yes-no signaling) were associated with less persistent disability at discharge and 20% of the entire cohort recovered all six target behaviors within the 6-week observation period.[26] The investigators also noted that for each behavior recovered, scores on the Disability Rating Scale (DRS),[27] which assesses degree of disability attributable to brain injury, improved by approximately two points.[26] In a retrospective analysis of 175 patients who were noncommunicative due to severe traumatic or nontraumatic brain injury and were followed across the first 8 weeks of inpatient rehabilitation, discernible yes-no

responses emerged at 6 weeks postinjury, on average.[28] By rehabilitation discharge, 61% of the sample had recovered the ability to communicate reliably. An important consistent finding across these studies is that these complex behaviors did not reemerge until after discharge from the trauma setting.[26]

Recovery of Function

In 2020, the Centers for Disease Control and Prevention and the National Institute on Disability, Independent Living and Rehabilitation Research (NIDILRR) issued a report on functional outcome between 1 and 5 years postinjury in a large (n = 4,838) cohort of participants with msTBI enrolled in the TBIMS National Database between 2001 and 2007.[29] The primary finding was that, for most participants, functional status was dynamic during this period, not stable. Key findings from the report are summarized below:

- 61% of participants experienced a change in global level of function- 26% improved, 39% remained stable, and 35% declined or died. Decline increased in association with increasing age with males older than 70 years showing the most decline.
- 57% of participants were independent at 1 year; however, 34% experienced a change in need for supervision with equal proportions needing more and less (i.e., 17% required more and 17% required less).
- 49% of participants required some cognitive assistance at both the 1- and 5-year follow-ups and nearly 50% experienced a change in cognitive function with equal proportions improving and declining (i.e., 24% improved and 24% declined).
- 17% of participants required some assistance with motor function at 1 year with 23% requiring assistance at 5 years. In general, motor function remained relatively stable (i.e., 8% improved and 13% declined).

Proportional weighting analyses demonstrated that the results reported in the CDC-NIDILRR report were representative of patients admitted to non-TBIMS rehabilitation hospitals in the United States, suggesting that TBI should be viewed as a chronic disease.

There is converging evidence from long-term outcome studies completed over the last decade that, even among patients with TBI who remain severely disabled during the acute hospitalization, approximately 20% of those who subsequently receive inpatient rehabilitation go on to regain functional independence at some point between 1 year and 10 years postinjury.[20–23,30–32]

In a cohort of 290 hospitalized patients from the TRACK-TBI network who were dependent on others for daily care at 2 weeks post-TBI and were followed for 12 months, 52% were functioning independently at home for at least 8 hours a day on the Glasgow Outcome Scale-Extended (GOSE)[33] by 1 year postinjury.[21] On the DRS,[27] approximately one in five reported no disability and another 14% had only mild disability.[21]

A TBIMS study that followed 108 patients with msTBI reported that by 5 years postinjury, nearly 20% of those who were following commands on admission were capable of living without in-house supervision and 19% were rated as employable.[22] Among those who were not following commands on admission but did so prior to discharge, 56% to 85% were independent in one or more domains of the Functional Independence Measure (FIM).[34] Even among those who failed to recover command-following by rehabilitation discharge, 19% to 36% achieved independence in at least one functional domain by 5 years postinjury.

Hammond and colleagues[30] conducted a 10-year follow-up study that included the same cohort of TBIMS participants described above in the 5-year outcome study.[22] Recovery of functional independence in self-care, mobility, and cognition was assessed using FIM[34] subdomain ratings and results were analyzed separately for participants who demonstrated early (<28 days) versus late (≥28 days) recovery of command-following. In all three FIM domains, both subgroups showed increases in the proportion of persons who achieved independence between 5 years and 10 years and decreases in the proportion of those who remained totally dependent. Among the early recovery subgroup, 88% to 100% were independent by 10 years, depending on subdomain, compared with 50% to 75% of those in the late recovery subgroup. Although significant late functional decline was not observed in this cohort, risk factors associated with functional decline in this population include lower education level, male sex, longer rehabilitation length of stay and age >25 years at the time of injury.[30] Figure 2 depicts the trajectory of long-term functional recovery based on data from the TBIMS National Database.

Few studies have investigated long-term functional outcome among patients who remain in VS/UWS or MCS longer than 6 months. While recovery of consciousness and behavioral improvement have been reported between 1 year and 5 years postinjury, severe to extremely severe functional disability is the most common outcome when these disorders persist for this length of time.[24,32] Findings are mixed as to whether injury etiology (i.e., traumatic vs. nontraumatic) influences functional recovery when VS/UWS and MCS persist beyond 6 months.[17,24,32]

RELATIONSHIP BETWEEN NEUROIMAGING, BLOOD-BASED BIOMARKERS, SOCIAL DETERMINANTS, AND FUNCTIONAL OUTCOME

Neuroimaging Biomarkers

Advances in neuroimaging have elucidated the pathophysiologic mechanisms that underly recovery of function after msTBI. While CT imaging remains the standard of care, MRI offers greater precision when classifying injury severity and predicting functional outcome. These improvements have been enabled by the development of common data elements (CDEs) for TBI neuroimaging, which are categorized into "basic," "descriptive," and "advanced" pathoanatomic features.[35] A prognostic validity study completed by the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) network found that the TBI neuroimaging CDEs provided excellent discrimination between patients who had favorable versus unfavorable outcomes at 6 months on the dichotomized GOSE.[36] The greatest amount of predictive value was contributed by the basic CDEs, which classify lesion types as present or absent. A commissioned issue of *Lancet Neurology* on TBI published in 2022[3] drew the following conclusions regarding TBI neuroimaging following a comprehensive, evidence-informed review:

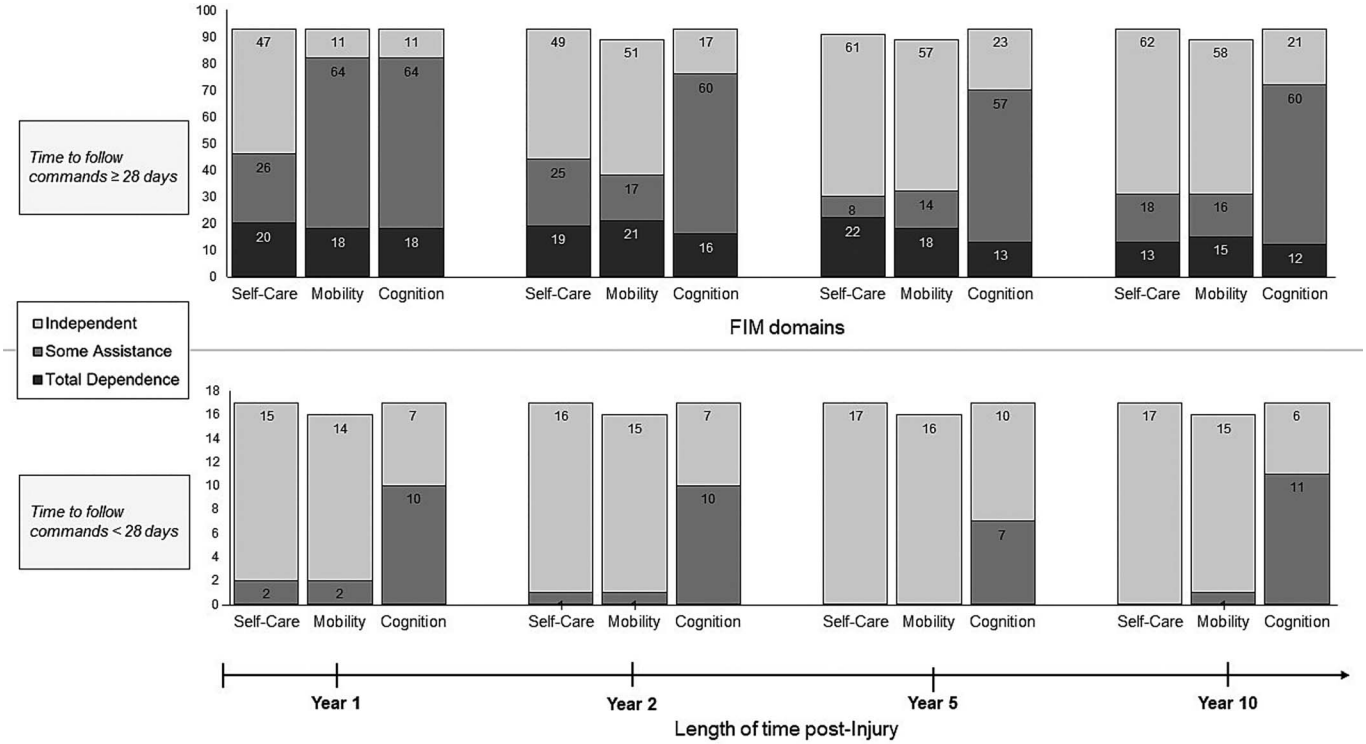

Figure 2. Long-term functional recovery trajectories in patients enrolled in the Traumatic Brain Injury Model System at 1 year, 2 years, 5 years, and 10 years postinjury. (Top Panel) Bars indicate the percentage of patients who were not following commands by 28 days postinjury (n = 93) who were independent (light gray), required some assistance (intermediate gray) or were completely dependent (dark gray) in self-care, mobility and cognitive activities at 1 year, 2 years, 5 years, and 10 years postinjury, based on FIM ratings. (bottom panel) Functional outcomes on the FIM for patients who regained command-following within 28 days postinjury (n = 17). Based on Hammond FM, Perkins SM, Corrigan JD, et al. Functional Change from Five to Fifteen Years after Traumatic Brain Injury. J Neurotrauma. 2021;38(7):858–869.

- Advanced MRI techniques (e.g., diffusion tensor imaging, susceptibility weighted imaging) are more sensitive than CT imaging at detecting superficial contusions, traumatic axonal injury and traumatic vascular injury.[37,38] Quantitative MRI, which relies on volumetric analyses, reductions in fractional anisotropy, and increases in mean diffusivity can identify injury that is inconspicuous by visual inspection of MR images.[39]
- Quantitative diffusion tensor imaging has strong predictive value when employed in patients with severe TBI, and may be useful in identifying the substrate responsible for DoC.[40] Functional neuroimaging (i.e., fMRI, FDG-PET) and electroencephalographic (fEEG) procedures have demonstrated some utility in detecting conscious awareness in patients with severe TBI who do not exhibit observable signs of consciousness on bedside examination. The degree of connectivity in the default mode network appears to be associated with recovery of consciousness. This relationship holds for both correlated and anticorrelated DMN structures.[41] The AAN-ACRM-NIDILRR DoC practice guidelines recommend that multimodal neuroimaging be considered when behavioral findings are confounded or ambiguous but caution that negative findings should not be interpreted as evidence that the patient is unconscious.[42]

Blood-Based Biomarkers

Although not yet in widespread clinical use, blood-based biomarkers are expected to become a routine part of TBI assessment. Clinical indications include classification of injury severity, prognostication, and monitoring recovery. A panel of TBI biomarkers has been identified that reflects the pathophysiology of trauma-induced brain injury observed in the acute, subacute and postacute phases of recovery (Table 1).[43] While blood-based biomarkers hold the promise of high specificity when compared with clinical signs and symptoms, an important limitation is that these markers may be elevated by factors unrelated to the direct effects of the TBI.

The TRACK-TBI network has explored the clinical utility of TBI biomarkers across multiple studies. Glial fibrillary acidic protein (GFAP) and C-terminal hydrolase L1 (UCH-L1) are of particular interest as they have demonstrated discriminative ability in detecting TBI, grading injury severity and predicting downstream functional outcome.[44,45] The performance of a GFAP and UCH-L1 biomarker battery for early diagnosis of TBI was evaluated in 206 prospectively enrolled patients with mild to severe TBI and 175 healthy volunteers.[45] While neither biomarker had adequate sensitivity or specificity for detecting TBI, combining serum levels of both biomarkers distinguished patients with TBI from healthy controls (area under the curve = 0.94 compared with 0.87 and 0.91 for UCH-L1 and GFAP, respectively).

Vascular injury is a common sequela of TBI, leading to interest in identifying blood-based biomarkers of cerebral microvascular injury. At least 16 different biomarkers associated with traumatic microvascular injury have been identified, including von Willebrand factor (vWF), cellular cibronectin (c-Fibronectin),

TABLE 1. TBI Biomarker Profiles

Biomarker	Pathophysiologic Process	Recovery Phase	Time Scale	Time to Peak Elevation	Context of Use
Ubiquitin C-terminal hydrolase-L1 (UCH-L1)	Neuronal cell body injury	Acute	Minutes to days	<1 h	Prediction of mortality and long-term outcome
Neuron-specific enolase (NSE)					Detection of TBI
GFAP	Astroglial injury	Acute	Minutes to days	<1 h	TBI severity classification/prediction of CT abnormality
S100b protein					Detection of TBI/concussion
Neurofilament light protein	Delayed axonal injury/ demyelination	Subacute	Minutes to days	<1 wk	Prediction of mortality and cognitive decline
Myelin basic protein					Detection of TBI
All-spectrin breakdown products (SPBD120)	Apoptosis	Subacute	Minutes to weeks	<1 wk	Detection of TBI/concussion
Total-tau (T-Tau)/phosphorylated tau (P-Tau)	Neurodegeneration	Chronic	Minutes to years	<1 d + > 6 mo	Neurodegenerative disease risk/indicator of chronic TBI sequelae
Amyloid beta peptides (AB)					

thrombomodulin, endothelium specific receptor tyrosine kinase receptor (Tie2), angiopoietin 1 (Ang1), angiopoietin 2 (Ang2), vascular endothelial growth factor receptor 1 (Flt-1), placental growth factor (PIGF), vascular endothelial growth factor A (VEGF-A), VEGF-C, VEGF-D, E-selectin, platelet-derived growth factor receptor ß (PDGFR-ß), P-selectin, vascular cell adhesion protein 1 (VCAM-1), and basic fibroblast growth factor (bFGF).[46] TRACK-TBI investigators obtained plasma levels of biomarkers associated with microvascular injury within 24 hours of injury in 159 TRACK-TBI participants with mild to severe TBI (GCS, 3–15).[46] The relationship of biomarker levels to TBI severity and outcome on the GOSE at 3 months and 6 months postinjury was evaluated. Two distinct biomarker clusters emerged on principal components analysis. The first cluster of biomarkers, including Ang-1, bFGF, P Selectin, VEGF-C, VEGF-A, and Tie2, is associated with mechanisms of vascular repair and neuroprotection. The second biomarker cluster, including Ang-2, E-Selectin, Flt-1, P-Selectin, PIGF, thrombomodulin, and VCAM-1, has been implicated in endothelial apoptosis and breakdown of the blood-brain barrier[47] and, as such, appears to reflect injury severity. It should be noted that the majority of participants in the sample studied had GCS scores between 13 and 15. As noted by the investigators, further validation of the cerebral microvascular biomarkers may help inform the development of therapies based on injury mechanism.

The prognostic value of GFAP and UCH-L1 was explored in a second TRACK-TBI study that included 1,696 patients with mild to severe TBI.[44] Plasma samples of GFAP and UCH-L1 obtained on the day of injury predicted unfavorable outcome (GOS-E ≤ 4) and death (GOS-E = 1) at 6 months with good to excellent discriminative ability. However, prognostic accuracy was poor for predicting incomplete recovery (GOSE ≤8). Unlike the prior TRACK-TBI study,[45] combining the UCHL-1 and GFAP did not significantly improve the prognostic accuracy of either biomarker alone. Adding day-of-injury GFAP and UCH-L1 levels to existing prognostic models, such as IMPACT,[48] which includes demographic, injury severity, secondary insults, CT characteristics and laboratory values, can provide a more accurate estimation of the likelihood of unfavorable outcome, including death, after msTBI.[44]

Social Determinants

The type of postacute rehabilitation patients receive following discharge from acute care is an important predictor of long-term mortality and subsequent functional outcome.[49] Inpatient rehabilitation services are associated with improved long-term functional outcomes, lower mortality, and higher chances of regaining independence at home.[50] Systemic racism, associated with racial and socioeconomic disparities, and decreased access to high-quality care lead to poorer outcomes after traumatic injury.[51–54] Evidence consistently indicates that, following msTBI, Black, Indigenous, and other People of Color (BIPOC) have higher mortality, score lower on the FIM and DRS measures, and receive poorer services in both quantity (less time in physical, occupational, speech, and neuropsychological therapy) and quality (less intense occupational, speech, and vocational therapy).[55]

Healthcare regulations, insurance policy, and hospital admission criteria may limit access to inpatient rehabilitation on the basis of disability severity. A highly cited study from the TBIMS Program that combined existing national datasets estimated that only 13% of persons aged 16 and older with msTBI gain access to inpatient rehabilitation, yet, 40% to 50% of persons with msTBI have persistent disability at 1 year.[56] Against this backdrop, Centers for Medicare and Medicaid Services (CMS) has established inpatient rehabilitation admission criteria requiring that patients must be able to actively participate in 3 hours of therapy, five to seven times a week.[57] This policy has been incorporated into McKesson's InterQual criteria[58] to determine medical necessity for inpatient rehabilitation, but disincentivizes these facilities to admit patients who cannot actively participate in rehabilitation for fear of disqualification and financial penalty, despite evidence of favorable long-term outcome in a substantial proportion of these patients.[50]

Recent narrative reviews have highlighted inequities for Black and Hispanic/Latinx Americans who face disparities in referral processes and access to rehabilitation services.[59,60] Racial disparities in access to inpatient rehabilitation persist for people of color with TBI regardless of insurance status, bringing about worse functional outcomes and reduced quality of life. In a retrospective 6-year study that used discharge records from the Nationwide Inpatient Sample (NIS), the largest all-payer sample of inpatient discharge data, 70% of people who were White, 70% of those who were Asian, 59% of those who were Black, and 49% of those who were Hispanic had insurance.[61] Even insured Black, Asian, and Hispanic patients had decreased chances of discharge to rehabilitation compared with insured White

counterparts, controlling for patient- and hospital-level variables. Compared with insured White people, uninsured people of all races were less likely to be discharged to rehabilitation.

EVIDENCE-BASED TREATMENT INTERVENTIONS FOR MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

Rehabilitative Care in the Acute Setting

The incidence of ICU-acquired of immobility/weakness (20–60%), delirium (50–80%), pain (50%), and psychiatric symptoms (20–30%), including depression, anxiety, and posttraumatic stress disorder, is high.[62–64] The American College of Surgeons (ACS) Verification, Review, and Consultation (VRC) Program outlines standards that are used to evaluate the commitment, readiness, resources, policies, patient care, and performance improvement activities of trauma centers. These standards, summarized in the 2022 edition of *Resources for Optimal Care of the Injured Patient,*[65] include criteria for provision of rehabilitation services during and after the acute phase of care. The standards explicitly require trauma centers to have protocols in place that enable multidisciplinary assessment for early determination of rehabilitation needs and provision of appropriate rehabilitation services during the acute phase of care to ensure optimal functional recovery. Measures of compliance include documentation that rehabilitation needs were assessed, and an interdisciplinary plan of care implemented in a timely manner.

The VRC standards are based on evidence that early multidisciplinary rehabilitation is safe, feasible, cost-effective[66–68] and yields more effective results when initiated acutely and provided continuously.[69] When implemented early (i.e., prior to medical stability, during mechanical ventilation), rehabilitation interventions have been shown to mitigate complications of critical illness, which can persist for up to 2 years postinjury.[70,71] Unfortunately, published estimates suggest that only about one-third of patients who report cognitive and psychological impairments receive interventions in these areas[72,73] and those who experience discontinuity of rehabilitation care between the acute and postacute phase have poorer functional outcomes than those who receive continuous rehabilitation.[74,75]

The VRC standards also require that trauma centers have a process in place to determine the level of care patients require following discharge and the specific rehabilitation services needed at the next level of care. This is particularly important for patients with msTBI who may require specialized rehabilitation for cognitive, visuoperceptual, and behavioral sequelae. The standards also emphasize that transition procedures adopt a person-centered approach, which may include peer-to-peer mentoring, participation in the American Trauma Society's Trauma Survivors Network program and continuous case management that links trauma center services with community care. The importance of appropriate discharge planning and rehabilitative care is illustrated by the results of a large retrospective trauma study, which found that cumulative mortality at 3 years postdischarge was significantly lower for patients discharged home or to inpatient rehabilitation facilities relative to those discharged to skilled nursing facilities.[76]

Management of Posttraumatic Amnesia and Confusional State

Recent evidence suggests that it is possible to accelerate the pace of recovery from PTA[77,78] and PTCS,[13] highly disabling syndromes that limit the effectiveness of rehabilitative interventions. This phase of recovery is marked by disturbance in arousal, impaired attention, disorientation, anterograde and retrograde amnesia, and marked fluctuation in cognition and behavior.[13,79] The duration of PTA is measured from the time of injury until the individual regains the ability to store and retrieve new information.[80] Evidence-based guidelines for management of PTA derived from a systematic review of the literature performed by an international consortium of TBI experts recommended the following treatment strategies[81]:

- Daily assessment of PTA using standardized scales, such as the Westmead Post-Traumatic Amnesia Scale (WPTAS),[82] until PTA resolution.
- Maintain a secure, quiet, and consistent environment, limiting overstimulation, and providing rest as needed to manage and minimize agitation and confusion.[81]
- Minimize use of physical restraints.
- Communicate using clear and simple language.
- Present familiar information as tolerated and identify and address triggers for agitation.
- Educate family members on how to best engage with the patient to promote orientation and minimize agitation.
- Rehearse activities of daily living (ADLs) to exploit procedural memory functions, which are preserved during PTA/PTCS.

A randomized controlled trial involving 104 patients with severe TBI who remained in PTA for >7 days and were admitted to rehabilitation exposed participants to either physical therapy and/or speech therapy alone (treatment as usual), or treatment as usual plus daily ADL retraining (treatment) while they were in PTA.[83] The FIM[34] served as the primary outcome. Participants in the treatment group achieved functional independence significantly faster than those who received treatment as usual and demonstrated significantly greater functional improvement from baseline to PTA emergence and at rehabilitation discharge. This difference was no longer apparent at the 2-month follow-up, in part, because 60% of the sample attained the maximum FIM score by discharge. Notably, inpatient length of stay was 15 days shorter, on average, in the treatment group. These findings demonstrate that patients can benefit from procedural learning strategies mediated by the implicit memory system during florid PTA.

Cognitive Rehabilitation

Cognitive rehabilitation is a systematic, therapeutic approach to the assessment and treatment of cognitive impairment after TBI.[84] This approach emphasizes strategies such as reinforcing or reestablishing learned behavioral patterns, establishing new cognitive patterns or strategies through compensatory mechanisms, and helping patients adapt to cognitive disability. Cognitive domains addressed through cognitive rehabilitation include but are not limited to attention, language and communication skills, memory, visuoperception, and executive function. The effectiveness of these interventions is heavily influenced

by patient characteristics, most notably, severity of cognitive impairment and length of time postinjury. This analysis drives which interventions are suitable for use in the acute care setting and which are not. Ultimately, the goal of cognitive rehabilitation is to improve global level of function and life satisfaction.[84]

A series of evidence-based reviews on the effectiveness of cognitive rehabilitation completed by the American Congress of Rehabilitation Medicine (ACRM) strongly suggest that the right treatment provided to the right person at the right time can aid recovery and minimize physical and psychological comorbidities.[84–87] Findings suggest that attentional deficits can be addressed through a combination of direct-attention training and metacognitive strategy training. For example, direct attention training identifies and addresses specific attention impairments[87] by teaching self-monitoring strategies, providing performance feedback, and conducting educational activities centered on the functional consequences associated with attention deficits. Metacognitive training techniques such as Time Pressure Management (TPM) can be employed to help patients compensate for reduced processing speed and regulate information input, thereby improving their ability to complete everyday tasks independently.[87] Memory impairments can be addressed through "internalized" self-regulatory strategies, which rely on self-instruction and self-monitoring,[87] or "external" compensatory strategies, such as the use of memory aids (e.g., notebooks), which have been shown to be effective for patients with moderate to severe memory impairment related to TBI.[87] Generalization to everyday activities is best achieved when training activities are conducted in functional contexts.

Executive function impairments can also be managed through metacognitive strategy training, which incorporates formal training in problem solving and goal management. For patients presenting with severe cognitive deficits, errorless learning, which emphasizes successful task completion and avoidance of errors, can enhance performance on functional tasks that are directly targeted.[88] Remediation of impairments in communication and social cognition includes training in pragmatic conversational skills,[86,87] which focuses on comprehension and expression of both nonverbal (e.g., recognition of emotions from facial expressions) and verbal forms of communication. Table 2 summarizes

TABLE 2. Summary of Practice Standards, Guidelines, and Options for Cognitive Rehabilitation Post-TBI

Cognitive Domain	Practice Standards, Guidelines, Options	Additional Specifications
Attention	Utilization of direct-attention training and metacognitive strategy training to increase task performance and promote generalization to daily functioning.*	Recommended for use during postacute rehabilitation, but there is no indication that incorporation during acute rehabilitation has adverse effects.
	Direct-attention training for specific modular impairments in working memory, including the use of computer-based interventions, should be considered to enhance both cognitive and functional outcomes.**	
Memory	Utilization of internalized strategies (e.g., visual imagery, association techniques) and external memory compensations (e.g., notebooks, electronic technologies).*	Recommended for patients with mild memory impairment.
	Use of external compensations with direct application to functional activities.**	Recommended for patients with severe memory impairment.
	Errorless learning techniques may be effective for learning specific skills or knowledge, with limited transfer to novel tasks or reduction in overall functional memory problems.†	Recommended for patients with severe memory impairment.
	Group-based interventions may be considered for remediation of procedural memory and recall of information used in the performance of everyday tasks.†	Recommended for patients with mild memory impairment.
Communication and social cognition	Training in interventions for functional communication deficits (e.g., pragmatic conversational skills) and recognition of emotions from facial expressions.*	Sole reliance on repeated exposure and practice on computer-based tasks without direct involvement and intervention by a therapist is not recommended.
	Cognitive interventions for specific language impairments (e.g., reading comprehension and language formulation).**	
	Group-based interventions may be considered for remediation of social communication deficits.†	
	Computer-based interventions as an adjunct to clinician-guided treatment for remediation of cognitive-linguistic deficits.†	
Executive function	Metacognitive strategy training (e.g., self-monitoring emotions and self-regulation of behavior), which may incorporate formal protocols for problem solving and goal management in the setting of daily functional activities.*	All metacognitive strategies are recommended for use during postacute rehabilitation in patients with mild to moderate executive impairment.
	Metacognitive strategy training should be incorporated into occupation-based treatment for practical goals and functional skills.**	Recommended for patients with severe executive function impairments.
	Explicit (e.g., verbal-and-video) performance feedback as a form of metacognitive strategy training for individuals with impaired self-awareness.**	
	Group-based interventions for remediation of deficits in awareness, problem solving, goal management and emotional regulation.†	
	Use of skill-specific training (e.g., errorless learning) to promote performance of specifically trained functional tasks with no expectation of transfer to untrained activities.†	

*Practice standards are based on at least 1, well-designed Class I study with an adequate sample, or overwhelming Class II evidence.
**Practice guidelines are based on 1 or more class I studies with methodological limitations, or well-designed class II studies with adequate samples.
†Practice options are based on class II or class III studies.

the practice standards, guidelines and options recommended by ACRM by cognitive domain and contextual factors.

Pharmacologic Treatment

While a variety of neurostimulant medications have been used in patients with msTBI, few studies have systematically investigated their effectiveness during the acute phase of recovery. No agent has been shown to be effective in neuroprotection,[89] and only one, amantadine hydrochloride (AH), has been demonstrated effectiveness during the postacute period.[90]

A retrospective analysis of frequency of use of AH, methylphenidate, and modafinil among 608 patients with TBI admitted to the ICU at two Level 1 Trauma Centers found that only 8% received a stimulant.[91] Amantadine was most commonly prescribed (85.4%) followed by modafinil (14.6%). Methylphenidate was not prescribed to any patients. Low arousal was the most commonly documented indication at 73% with the median time to stimulant initiation at 11 days postinjury (range, 2–28 days). The median GCS[5] score at the time of drug initiation was 9 and ranged from 4 to 15. Approximately 15% of patients required the dose to be reduced or discontinued during the admission.

Amantadine Hydrochloride

AH is an N-methyl-D-aspartate (NMDA) receptor antagonist that has antiexcitotoxic effects and is believed to upregulate selective dopaminergic pathways.[92] AH is the only medication proven to accelerate the pace of recovery after severe TBI[90] earning it a Level A rating (i.e., *should* be administered) for treatment of patients with DoC in the 2018 American Academy of Neurology-American Congress of Rehabilitation Medicine-National Institute on Disability Independent Living and Rehabilitation Research practice guidelines for management of DoC.[42] In an 11-site international RCT, patients in VS or MCS (n = 184) who were between 4 weeks and 16 weeks postinjury received AH (200–400 mg twice a day) or placebo for 4 weeks followed by a 2-week washout period. The AH group demonstrated significantly lower scores on the DRS[27] (i.e., less disability) after 4 weeks of treatment relative to those who received placebo and there was no difference in the frequency of adverse events between the two groups.[90]

A single-center, double-blind, randomized, controlled trial that included patients with GCS[5] scores between 3 and 9 received AH or placebo at 100 mg twice a day for 6 weeks.[93] Participants were assessed on Day 1, Day 3, Day 7 and at 6 months postdrug. The change in GCS score from day 1 to day 7 was significantly higher in the AH group and there was no significant difference in adverse events. No other differences in outcome were observed, including degree of disability at 6 months.

A meta-analysis of 14 clinical trials and six observational studies involving 512 patients with severe TBI, 325 with moderate TBI, 75 with severe or moderate TBI and 165 with unknown severity found that AH significantly improved cognitive function relative to controls, especially when the intervention began in the first week after TBI and continued for less than a month.[94]

Zolpidem

Zolpidem is a sedative-hypnotic agent that has been observed to have paradoxical effects when administered to some patients with DoC.[95] Zolpidem is believed to promote recovery of consciousness by reversing bilateral anterior forebrain hypometabolism in the frontal/prefrontal cortex, thalami and striatum.[96] The only controlled zolpidem trial conducted in a TBI population involved 84 adults who were in traumatic or nontraumatic VS or MCS for more than 4 months postinjury. In this double-blind crossover RCT, participants were evaluated on the CRS-R[97] before and after receiving either 10 mg of zolpidem or placebo. Only 5% participants were determined to be "responders," based on an increase of 5 or more points on the CRS-R relative to pre-drug baseline.[98] The majority of adverse events (83%) occurred in the zolpidem group but all but one were rated as mild and resolved without specific management.

Methylphenidate

Methylphenidate (MPH) is a sympathomimetic dopamine agonist that binds to presynaptic transporters, inhibiting reuptake of both dopamine and norepinephrine.[99] A meta-analysis of 17 studies (i.e., placebo-controlled crossover or RCT) including 462 adults with TBI evaluated the effects of MPH on cognitive outcome and found that MPH significantly improved processing speed, but had no effect on working memory, sustained attention, or mental control. Adverse event analysis indicated that MPH was associated with increased heart rate.[100] Major limitations of the study were that MPH dosage and frequency ranged from a single dose of 20 mg to 30 mg to a titrated dose extending to 30 weeks and all but two of the 17 studies were conducted on patients who were 2 months or more postinjury.

To our knowledge, only one study has investigated the effects of methylphenidate (MPH) alone on patients undergoing ICU care after msTBI with a focus on accelerating recovery of consciousness.[101] A prospective randomized double-blind trial involving 40 patients with severe TBI (GCS = 5–8) and 40 with moderate TBI (GCS = 9–12) were randomly assigned to receive either 20 mg of MPH twice a day or placebo beginning on the day of admission. In the severe TBI group that received MPH, the length of the ICU stay was 3 days shorter while the total hospital stay was reduced by 4.25 days. In the MPH-treated moderate TBI group, the ICU stay was 1.5 days shorter, but there was no significant reduction in total hospital length of stay.

Two ICU-based MPH clinical trials have recently been launched that may advance current knowledge of clinical effectiveness. The STIMPACT trial is using predictive biomarkers based on connectome maps as a sample enrichment strategy to select patients with acute severe TBI for IV MPH.[102] This study has also incorporated pharmacodynamic biomarkers to measure therapy-induced changes in cortical networks that mediate consciousness. A second placebo-controlled, randomized, crossover study in Europe is testing the effects of a 20 mg dose of MPH or placebo on automated pupillometry, neurovascular coupling measured by near-infrared spectroscopy combined with electroencephalography and level of consciousness in patients diagnosed with traumatic or non-TBI coma, VS/UWS or MCS in the ICU.[103] Both trials are promising in view of their use of biomarkers to inform targeted individualized treatments.

Noninvasive Brain Stimulation

Noninvasive brain stimulation (NBS) techniques, particularly transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), offer a potentially promising

alternative to pharmacologic treatments for TBI with lower risk of side effects.[104–106] While these interventions have primarily been utilized in the postacute phase of TBI recovery, their presumed mechanism of action aligns with the acute pathophysiologic effects of TBI. During the acute phase following injury, the excitotoxic cascade of events brought about by excessive release and accumulation of glutamate, cerebral ischemia and elevated lactate levels causes metabolic stress, inflammation, mitochondrial dysfunction and apoptosis.[107] Appropriate configuration of NBS parameters may mitigate the acute glutamatergic hyperexcitability triggered by TBI and facilitate adaptive neuroplasticity.[108]

Transcranial Direct Current Stimulation

Transcranial direct current stimulation applies a low-intensity electric current through two electrodes placed on the head, modulating neuronal resting membrane potentials.[109] Depending on the size and location of the electrodes, tDCS may focally suppress or facilitate neuronal firing. This modulation of cortical activity can boost adaptive neuroplasticity, increasing dendritic spines and strengthening synaptic connections.[109–113] While anodal tDCS depolarizes neurons and increases cortical excitability, cathodal tDCS produces neuronal hyperpolarization, decreasing cortical excitability. Both techniques can enhance motor, language, and memory performance.[114,115]

A double-blind sham-controlled randomized crossover study tested the effectiveness of a single 20 minute session of anodal tDCS applied to the left dorsolateral prefrontal cortex in 55 patients diagnosed with VS (n = 25, TBI = 6) or MCS (n = 30, TBI = 19), 8 of whom were between 7- and 30 days postinjury.[116] In the MCS group, 43% (13/30) of participants showed at least 1 behavioral sign of consciousness not previously observed after tDCS treatment. In the VS/UWS group, 8% (2/25) of participants who were <3 months postinjury demonstrated signs of consciousness (i.e., command-following, visual pursuit) that were not observed during sham stimulation or before exposure to tDCS. The behavioral changes were associated with increased functional connectivity in the default mode and frontal-parietal associative networks, which mediate internal and external awareness, respectively. There was, however, no correlation between tDCS response and outcome on the GOSE at 12-month follow-up. No tDCS-related side effects were observed suggesting this procedure can be used safely in properly selected patients during the acute period.

Transcranial Magnetic Stimulation

In TMS, a copper wire coil connected to a magnetic stimulator generates an electromagnetic pulse that induces focalized neural depolarization and firing.[117] The magnetic pulses pass through the skull and create electric currents in focal brain regions. When trains of stimuli are delivered repetitively to targeted brain regions (rTMS), cortical processes can be suppressed or facilitated based on stimulation parameters. Continuous low frequency rTMS decreases cortical excitability while intermittent high frequency rTMS enhances excitability.[118] Thus, rTMS can be applied to either prime or inhibit neural responsiveness, providing an opportunity to modulate cognition and behavior.[119]

More than 20 studies have investigated therapeutic applications of rTMS in patients with TBI-related DoC, cognitive impairment, depression, pain, auditory dysfunction, motor impairment, dizziness, and headache. Most of the available evidence is based on single case studies, case series and small single center observational studies conducted during the postacute phase of recovery and the evidence for effectiveness is mixed.[120] One exception is a recently completed randomized, double-blind, placebo-controlled trial involving 99 patients who were recruited from the neurosurgery department, ICU or rehabilitation unit of a Chinese university hospital and were between 1 month and 3 months postinjury.[121] Participants were assigned to either the treatment, control, or placebo group. The experimental group received conventional rehabilitation treatment and high frequency rTMS (20 Hz) over M1 of the affected hemisphere, the control group received conventional rehabilitation treatment and conventional rTMS (20 Hz) over the left dorsolateral prefrontal cortex and the placebo group received conventional rehabilitation treatment and sham rTMS. Participants were treated once a day, 5 days a week for 4 weeks. While there were no differences in GCS or CRS-R scores between the 3 groups at pretreatment, there were significantly greater increases in both GCS and CRS-R total scores at posttreatment in the experimental group compared to the control and placebo groups. Treatment effects were attributed to increased activation of the cerebral cortex at M1 through increases in cerebral blood flow speed and improvements in electrophysiologic resonance.

CONCLUSION

Understanding the natural history of recovery from msTBI is essential to accurate prognostication, appropriate treatment planning and effective family counseling. Recent longitudinal research has clarified that functional recovery can occur well after discharge from the ICU, extending up to 10 years postinjury. These findings challenge the nihilistic beliefs that persist among clinicians and other stakeholders about the prospects for meaningful recovery. Advances in neuroimaging and blood-based biomarkers are beginning to re-shape approaches to classifying injury severity, outcome prediction and treatment selection. Early access to multidisciplinary rehabilitation is an essential component of acute clinical management as recognized in the recently updated ACS Verification, Review, and Consultation Program standards for trauma centers. Treatment alternatives shown to be effective during the acute phase of recovery remain limited, however, empirically based protocols for management of PTA and PTCS, cognitive rehabilitation and pharmacological treatment should be considered in accord with recommended practice guidelines. Promising applications of noninvasive brain stimulation are emerging but require further study before they are routinely incorporated into clinical practice.

DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D605).

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