Application of Hyperbaric Oxygen Therapy in Traumatic Brain Injury

Comprehensive Clinical Practice Guidelines

The Sagol Center for Hyperbaric Medicine and Research, Shamir Medical Center, Tel-Aviv University, Israel

March 2025

Content

1. Introduction

Traumatic brain injury (TBI) represents one of the most significant public health challenges worldwide (1). The long-term sequelae of TBI can result in persistent cognitive, physical, and psychological impairments that significantly impact quality of life, productivity, and societal integration (2).

Hyperbaric oxygen therapy (HBOT) has emerged as a promising therapeutic intervention for patients with chronic symptoms following TBI (3). This treatment modality involves the administration of 100% oxygen at pressures greater than one atmosphere absolute (ATA) in a pressurized chamber. The physiological and cellular responses to HBOT have demonstrated potential for neurological recovery through mechanisms including enhanced tissue oxygenation, reduced inflammation, promotion of neuroplasticity, stimulation of angiogenesis, and modulation of cerebral metabolism (4).

These revised guidelines, updated in 2025, provide a comprehensive framework for clinicians to identify appropriate candidates for HBOT following TBI, establish standardized treatment protocols, and implement evidence-based assessment measures to evaluate outcomes. This document incorporates the latest research findings, clinical experience, and technological advances to optimize the application of HBOT in the management of TBI.

2. Pathophysiology of TBI and HBOT Mechanisms

2.1 TBI Pathophysiological Cascade

The pathophysiology of traumatic brain injury (TBI) involves complex biomechanical, cellular, and metabolic processes that evolve from the moment of impact through acute and chronic phases. Understanding these mechanisms is essential for implementing effective therapeutic interventions such as hyperbaric oxygen therapy.

The biomechanical forces in TBI primarily involve rapid acceleration-deceleration and rotational forces acting on the brain within the skull. The grey matter-white matter junctions, particularly in the frontal and temporal lobes, are most susceptible to injury due to their distinct biomechanical properties (5). Different injury types create unique patterns of damage: impact injuries primarily affect cortical structures at the site of

impact and countercoup locations, while blast injuries generate rapid intracranial pressure fluctuations and cavitation phenomena, particularly at cerebrospinal fluid-brain interfaces.

The acute pathophysiological cascade begins with mechanical disruption of neuronal membranes, triggering dysregulated ion flux, particularly calcium influx through mechanically sensitive ion channels. This ionic disturbance precipitates widespread release of excitatory neurotransmitters, notably glutamate and aspartate, further destabilizing cellular ionic homeostasis (6). These events create a metabolic crisis where increased energy demands for cellular repair coincide with compromised oxidative phosphorylation, creating a critical mismatch. Injured neurons resort to less efficient anaerobic glycolysis, resulting in insufficient ATP production to meet cellular demands.

Mitochondrial dysfunction serves as a central pathophysiological mechanism (7). Post-traumatic calcium overload in mitochondria triggers multiple pathological processes: disruption of oxidative phosphorylation, enhanced production of reactive oxygen species (ROS), and alterations in mitochondrial membrane permeability. These changes not only impair energy production but also contribute to cellular damage through oxidative stress.

The neuroinflammatory response, now recognized as a critical component of secondary injury, involves complex microglial activation patterns (8). Activated microglia release various inflammatory mediators, including cytokines and ROS, potentially establishing a state of chronic neuroinflammation. Recent research has elucidated that initial injury primes microglial responses, leading to exaggerated neuroinflammatory reactions to subsequent impacts (9). This explains the enhanced vulnerability to subsequent injuries, where even mild secondary impacts can trigger disproportionate neurological deterioration.

Microvascular injury occurs predominantly at grey-white matter junctions, leading to regional perfusion deficits that persist beyond the acute phase (10). This contributes to ongoing tissue hypoxia and metabolic dysfunction. Neurovascular coupling and autoregulation disruption following TBI are particularly significant, with impaired

cerebrovascular reactivity potentially persisting for months post-injury and contributing to symptom chronicity(11) .

The reduced cellular metabolism resulting from these processes impacts synaptic plasticity, including decreased brain-derived neurotrophic factor (BDNF) expression and altered neurotransmitter dynamics(12) . Persistent alterations in neural network activity and connectivity patterns can be demonstrated even months post-injury (13, 14). Longitudinal studies have documented that persistent metabolic dysfunction correlates with progressive neurodegeneration and network disconnection, particularly in cases of repetitive injury (14).

While most individuals recover from mild TBI within days to weeks, approximately ***15-25% of patients experience persistent post-concussion symptoms*** due to these complex neurometabolic cascades (15). ***In approximately 20-30% of those with persistent symptoms, post-concussion syndrome (PCS) develops,*** characterized by symptoms lasting beyond three months post-injury (16). Advanced neuroimaging techniques have revealed that if symptoms persist at 3 months, there is a significantly higher likelihood of continuation at 12 months post-injury, though symptom trajectories are influenced by multiple factors including genetics, pre-existing conditions, and psychosocial determinants (17).

2.2 HBOT Mechanisms in TBI Recovery

Hyperbaric oxygen therapy represents a mechanistic intervention targeting these fundamental pathophysiological processes (18). The administration of 100% oxygen at pressures exceeding 1 atmosphere absolute (ATA) achieves arterial O_2 tensions around 1500 mmHg, with tissue oxygen levels reaching 200-400 mmHg (19). This hyperoxic environment initiates multiple therapeutic cascades that address the underlying dysfunction.

The hyperoxic-hypoxic paradox underlies HBOT's therapeutic efficacy (4). Intermittent exposure to high oxygen levels triggers cellular pathways typically activated during hypoxia, particularly through hypoxia-inducible factors (HIFs) upregulation. This paradoxical effect promotes angiogenesis, mitochondrial biogenesis, and cellular repair mechanisms without the detrimental effects of chronic oxygen extremes.

HBOT exerts multiple mechanistic effects through interconnected pathophysiological pathways:

Tissue Oxygenation and Metabolism: HBOT demonstrates sustained enhancement of tissue oxygenation persisting 6+ hours post-session (20). This hyperoxic state optimizes aerobic metabolism, reducing lactate accumulation ($p<0.001$) and directly increasing cerebral metabolism rates through enhanced dissolved oxygen content. By providing supraphysiological levels of oxygen, HBOT addresses the fundamental energy crisis in injured brain tissue (21).

Neuroplasticity Activation: Oxygen-dependent mechanisms drive significant upregulation of neural stem cells and improved white matter integrity (22). Studies have documented increased BDNF expression following HBOT in animal models of brain injury (22), with corresponding improvements in neural stem cell proliferation and synaptic plasticity markers. DTI studies in human TBI patients have shown measurable improvements in white matter microstructure following HBOT treatment protocols .These changes support structural and functional neural recovery pathways (23).

Mitochondrial Function Restoration: BOT has been shown to enhance cellular energetics through improvements in mitochondrial function. Recent studies demonstrate that HBOT significantly increases ATP production while reducing oxidative stress markers in brain tissue following injury (24). Research has documented improvements in electron transport chain efficiency and decreased mitochondrial ROS production following HBOT treatment protocols (25). This mitochondrial recovery addresses one of the primary pathological mechanisms in TBI and provides a cellular basis for the observed clinical improvements.

Vascular Remodelling and Angiogenesis: The hyperoxic-hypoxic paradox induced by HBOT promotes significant angiogenesis and increases vascular density, with corresponding improvements in tissue perfusion indices (26)). Research has demonstrated that HBOT upregulates VEGF expression, supporting enhanced regional cerebral blood flow essential for neurogenesis and synaptogenesis (27). This vascular improvement helps restore adequate perfusion to previously hypoperfused regions in the injured brain (28). The resulting enhancement in cerebral blood flow provides a critical foundation for tissue recovery following traumatic brain injury .

Anti-inflammatory Mechanisms: HBOT demonstrates significant reduction in neuroinflammatory markers, including decreased microglial activation (Iba1 expression) and reduced astrogliosis (GFAP expression) (29). Studies show that HBOT attenuates pro-inflammatory cytokines including IL-1β and TNF-α (30).. Blood-brain barrier integrity improves through reduction in matrix metalloproteinase-9 expression, accompanied by reduced vasogenic edema (31). These effects help resolve the chronic inflammatory state that contributes to ongoing symptoms following traumatic brain injury (25).

Additional Benefits in Blast Injuries: In blast-related injuries, HBOT provides additional therapeutic benefit through bubble recompression effects, mitigating gas-related tissue damage that may be unique to this injury mechanism (32).

These mechanisms work synergistically to address the fundamental pathophysiological processes underlying persistent symptoms after TBI. HBOT does not simply treat symptoms but rather targets the underlying tissue dysfunction, potentially enabling more comprehensive recovery. Recent studies using advanced neuroimaging have demonstrated that clinical improvements following HBOT correlate with normalization of brain metabolism and connectivity, providing objective evidence of its neurotherapeutic effects (23, 28, 33, 34).

The therapeutic mechanisms of HBOT align precisely with the pathophysiological deficits present in TBI, providing a strong mechanistic rationale for its application in carefully selected patients with persistent symptoms. By addressing energy metabolism, neuroinflammation, vascular dysfunction, and neural repair simultaneously, HBOT offers a comprehensive approach to the complex pathophysiology of TBI rather than targeting isolated symptoms.

3. Evidence Base for HBOT in TBI

The evidence supporting HBOT for TBI, particularly for persistent post-concussion syndrome (PCS), has expanded significantly through high-quality randomized controlled trials (RCTs) and meta-analyses. A systematic review and meta-analysis of

30 studies, including 9 RCTs, provides a comprehensive evaluation of HBOT's efficacy in treating persistent PCS symptoms.

3.1 Meta-Analysis Findings

Recent meta-analysis of HBOT in post-concussion syndrome reveals significant treatment effects across multiple domains:

1. **Cognitive Function**: Analysis of six studies (N=304) demonstrated a moderate to large positive effect (pooled effect size g=0.78 [95% CI: 0.56, 0.99]) with acceptable heterogeneity (I^2=70.6%). Significant improvements were documented in memory, executive functions, attention, and information processing speed ($p<0.0001$).
2. **PTSD Symptoms**: Five studies (N=250) showed a moderate positive effect of HBOT on PTSD symptoms that commonly co-occur with TBI (pooled effect size g=0.57 [95% CI: 0.31, 0.82]) with moderate heterogeneity (I^2=69.8%).
3. **PCS Symptoms**: Eight studies (N=371) examining quality of life and symptom measures demonstrated high variability (I^2=85.1%), with individual study effects ranging from g=-0.07 to g=2.47, suggesting that response to treatment may depend on patient characteristics and protocol parameters.

3.2 Key Randomized Controlled Trials

Several high-quality RCTs provide strong evidence for HBOT's efficacy in chronic TBI:

Boussi-Gross et al. (34) conducted a civilian-focused crossover RCT including 56 patients with persistent PCS 1-6 years post-injury. Using validated computerized cognitive testing, they demonstrated significant improvements in memory ($p<0.0005$), executive functions ($p<0.0005$), attention ($p<0.005$), and information processing speed ($p<0.0001$). SPECT imaging provided objective validation of metabolic improvement correlating with cognitive enhancement.

Weaver et al.'s (35) Department of Defense-funded trial randomized 71 military personnel with PCS persisting 3 months to 5 years post-injury, comparing 40 daily HBOT sessions at 1.5 ATA versus 1.2 ATA air breathing. Significant

improvements were observed in post-concussion symptoms, neurobehavioral symptoms, and anger expression in the HBOT group. The Patient Global Impression of Change demonstrated significant advantage for HBOT (19/36) versus control (5/35) at 6 months. PTSD-comorbid patients showed more pronounced improvement.

Harch et al. (36) conducted an RCT of 50 military and civilian PCS patients utilizing a crossover design comparing 40 HBOT sessions (1.5 ATA) with an equivalent no-treatment period. Significant improvements occurred in post-concussion symptoms, PTSD manifestations, cognitive function, mood parameters, and quality of life metrics, with benefits persisting beyond three months post-treatment.

Hadanny et al. (37) performed a pediatric RCT investigating 25 children (ages 8-15) with persistent PCS 6 months to 10 years post mild-moderate TBI. Using a novel sham-controlled protocol (HBOT: 1.5 ATA, 100% oxygen vs. Sham: 1 ATA, 21% oxygen), with validated patient blinding, they demonstrated significant improvements in general cognitive scores ($p=0.01$), memory ($p=0.02$), executive function ($p=0.003$), and PCS symptoms. Mean diffusivity decreases in specific brain regions correlated with cognitive improvements.

Miller et al. (38) investigated 72 active military personnel with PCS persisting beyond four months, comparing 1.5 ATA HBOT, 1.2 ATA air breathing, and standard care. Both HBOT and low-pressure groups demonstrated significant symptom improvement compared to standard care, though without significant differences between intervention groups. This finding reinforced that pressures above 1 ATA constitute active treatment rather than true sham intervention.

Wolf et al. (39) conducted a double-blind study of 50 military servicemen comparing 2.4 ATA HBOT against 1.3 ATA intervention, demonstrating significant improvement in both groups for post-concussion and PTSD symptoms ($p=0.001$).

Cifu et al. (40) examined 61 active military servicemen with persistent PCS symptoms exceeding three months. The study compared three oxygen concentrations (75%, 100%, 10.5%) at 2 ATA, finding variable differences between groups in cognitive function, symptom questionnaire responses, and eye movement metrics.

Liu et al. (41) compared normobaric hyperoxia (NBH) and HBOT (2 ATA for 40 sessions) for mild TBI treatment beginning 24 hours post-injury. Both treatments significantly improved cognitive scores and reduced injury biomarkers compared to control ($p<0.01$), wit(39)h HBOT showing superior outcomes to NBH.

Ablin et al. (42) completed a prospective active-control study examining 64 mild TBI patients with fibromyalgia, comparing 60 HBOT sessions (2 ATA, 100% oxygen) with standard pharmacological treatment. Clinical improvements correlated with significant brain metabolism changes in left frontal and right temporal cortex regions as measured by SPECT imaging.

Weaver et al. (2025) (43) conducted a double-blind randomized trial examining 49 participants with persistent symptoms following non-stroke brain injury. Participants received either 40 hyperbaric oxygen therapy (HBOT) sessions at 1.5 ATA for 50 minutes or 40 sham sessions over 12 weeks, with all participants later offered 40 unblinded HBOT sessions. Significantly greater NSI score improvement was observed in the HBOT group compared to sham (mean difference 7.0, 95% CI [1.7-12.3], $p=0.01$), with improvements in olfaction, anxiety, sleep difficulties, and vestibular complaints. Following an additional 40 HBOT sessions, the original HBOT group demonstrated further NSI improvements at 12 months, suggesting cumulative benefits with 80 total sessions.

3.3 Neuroimaging Evidence

Objective evidence of HBOT's effects is provided by multiple studies using advanced neuroimaging techniques:

1. **SPECT Perfusion Imaging**: Studies consistently demonstrate normalization of cerebral blood flow in previously hypoactive regions, with improvements correlating with cognitive and symptom changes (34, 44).
2. **MRI Perfusion Imaging**: Studies utilizing dynamic susceptibility contrast (DSC) perfusion MRI have demonstrated significant cerebral blood flow increases following HBOT, particularly in limbic structures and hippocampal regions.These techniques provide quantitative measures of cerebral blood flow

without requiring radioactive tracers, allowing for safer longitudinal monitoring of treatment response (23, 28).

3. **Diffusion Tensor Imaging (DTI)**: Improvements in white matter integrity correlate with cognitive enhancement following HBOT (23) .

These neuroimaging findings provide objective validation of HBOT's effects beyond subjective symptom reporting, strengthening the evidence base for this intervention.

3.4 Protocol Considerations

The evidence suggests that effective HBOT protocols typically involve:

- Pressure range of 1.5-2.4 ATA
- 40-60 treatment sessions
- Treatment beginning at least 3-6 months post-injury for chronic cases

This substantial body of evidence, particularly from well-designed RCTs with objective outcome measures, provides robust support for HBOT as a treatment option for appropriately selected patients with persistent symptoms following TBI.

4. TBI Criteria for HBOT Eligibility

4.1 The Eligibility Formula

Patients will be eligible for HBOT based on the following comprehensive formula:

- *Documented TBI History*
- *Persistent Symptoms*
- *Functional Brain Imaging Findings*
- *Appropriate Patient Expectations*
- *Absence of Contraindications*

Each component of this formula requires specific assessment as detailed in the evaluation protocol section.

HBOT may be provided earlier in the recovery course for patients who exhibit severe symptoms and show limited response to standard rehabilitation approaches. However, HBOT is not recommended as a first-line therapy for patients with minimal symptoms due to the lengthy nature of the treatment and its associated costs.

The patient's case manager (typically the treating neurologist or rehabilitation physician) should assess the condition and available treatment options before referring for an HBOT treatment course.

The issue of compensation, such as disability benefits or other support provided by governmental authorities for TBI, can affect the course of recovery and motivation for treatment. Therefore, the intensive and demanding course of HBOT should ideally not be offered when compensation claims are still unresolved, as this may complicate assessment of treatment response.

4.2 Core Eligibility Requirements

A documented history of TBI (impact, blast, or penetrating) occurring at least 3-6 months prior to consideration for HBOT is required. The severity of TBI at the time of injury (mild, moderate, or severe) should not be used as exclusion criteria, as the chronic sequelae often do not correlate with initial injury severity. When available, medical records documenting the injury should be reviewed; however, for cases without medical documentation, collateral history from witnesses may be considered.

Patients must demonstrate persistent post-concussion symptoms that developed or worsened following the TBI event. A minimum of three symptoms from the post-concussion syndrome clusters should be present, causing functional impairment in daily activities and persisting despite standard management approaches.

Objective deficits must be present in at least one domain. These may include cognitive deficits documented on standardized testing (detailed below) or physical deficits (motor, balance, coordination, speech) on examination. These deficits should be consistent with expected consequences of the type of injury sustained.

Brain imaging must demonstrate functional/anatomical mismatch on appropriate studies, with abnormalities in brain regions corresponding to clinical deficits. Evidence

of potentially recoverable tissue (penumbra) should be present on functional imaging, as detailed in the imaging criteria section.

Patient factors including realistic expectations for treatment outcomes, motivation to participate in rehabilitation, absence of significant psychological barriers to treatment, and adequate social support during the treatment period are essential components of eligibility assessment.

4.3 Post-Concussion Syndrome (PCS) Symptom Clusters

Post-concussion symptoms can be categorized into four primary clusters:

Physical symptoms include headache, dizziness, fatigue, sleep disturbance, visual disturbances, phonophobia, photophobia, balance problems, tinnitus, nausea, sensitivity to motion, and physical exercise intolerance.

Cognitive symptoms encompass memory problems, difficulty concentrating, slow processing speed, executive function problems, word-finding difficulties, mental fogginess, reduced cognitive endurance, difficulty multitasking, increased distractibility, problems with sustained attention, disorganization, and cognitive fatigability.

Emotional and behavioral symptoms may include irritability, emotional lability, anxiety, depression, apathy, impulsivity, reduced stress tolerance, emotional numbing, personality changes, reduced emotional awareness, social withdrawal, and reduced frustration tolerance.

Autonomic and neuroendocrine symptoms can manifest as orthostatic intolerance, heart rate variability abnormalities, temperature dysregulation, excessive sweating, exercise intolerance, altered thirst perception, gastrointestinal disturbances, bladder dysfunction, altered appetite, and hormone imbalances.

4.4 Relative Exclusion Considerations

Several factors warrant additional evaluation before HBOT consideration. These include recent unexplained worsening of symptoms, dominant post-traumatic headache without other TBI symptoms, isolated mood or anxiety symptoms without cognitive or physical deficits, extensive pre-existing neurological or psychiatric disorders, active

substance use disorders, litigation or compensation-seeking as primary motivation, expectations for complete symptom resolution, and history of non-adherence to medical treatments. Active or recent suicidality requires thorough psychiatric evaluation before HBOT consideration.

Patients with active suicidal ideation, especially with intent or plan, should undergo comprehensive psychiatric stabilization before initiating HBOT treatment. For patients with a history of suicidal behavior, a risk assessment by a mental health professional should be completed, and appropriate safety plans must be in place before treatment begins.

These criteria should be applied comprehensively, recognizing that each patient presents with a unique pattern of symptoms, deficits, and psychosocial factors that influence eligibility.

5. Patient Evaluation Protocol

Hyperbaric Oxygen Therapy (HBOT) for Traumatic Brain Injury (TBI) requires daily sessions over an extended period and may temporarily exacerbate symptoms. Patient selection and thorough preparation are crucial to ensure safety and effectiveness.

Patients should receive comprehensive education about expected treatment effects, including both anticipated benefits and potential challenges such as sleep disruptions, anxiety, mood fluctuations, energy level changes, and cognitive variations. This education promotes adherence to the treatment regimen and helps manage expectations.

To support patients through the treatment process, cognitive and self-regulation techniques should be introduced before treatment begins and practiced during the course. These techniques help patients manage symptom fluctuations and maintain emotional equilibrium throughout therapy.

5.1 Clinical Evaluation

- The clinical evaluation begins with a comprehensive medical history, focusing on the TBI event details including mechanism, severity, duration of loss of consciousness, and post-traumatic amnesia. A clear timeline of symptom development and progression should be established, along with documentation

of prior treatments and their effectiveness. Pre-injury medical, neurological, and psychiatric conditions should be carefully reviewed, as should current medications and supplements.

Required Documentation:

- Documented TBI occurring at least 3-6 months prior to HBOT consideration
- Clear timeline of symptom development post-injury
- Documentation of prior treatments and effectiveness
- Complete review of pre-injury medical, neurological, and psychiatric conditions
- Comprehensive current medication list

- Physical examination should include a complete neurological assessment, cardiovascular and pulmonary evaluation, ENT examination with particular attention to tympanic membrane integrity, vital sign measurements including orthostatic testing, and general physical condition assessment.

5.2 Chest x-ray evaluation

Chest x-ray within 6 months, should be obtained to rule out pulmonary disease unsuitable for HBOT. Pulmonary function tests should be performed for patients with respiratory disease.

5.3 Additional evaluations based on clinical history

Cardiac evaluation for patients with cardiovascular disease, ophthalmic examination for patients with history of eye disease, medication review for potential interactions, assessment of anxiety level and claustrophobia risk, blood glucose monitoring protocol for diabetic patients, dental evaluation to rule out potential barotrauma risk, and neurological assessment for seizure risk.

Absolute HBOT contraindications that must be ruled out include unhealed large skull fractures or defects, untreated pneumothorax, concurrent use of certain

chemotherapeutic agents, severe untreated claustrophobia, uncontrolled seizure disorders, untreated pneumothorax, severe pulmonary disease with CO2 retention, severe pulmonary disease with CO2 retention, and pregnancy in the first trimester.

5.4 Laboratory evaluation

Laboratory testing should include complete blood count, comprehensive metabolic panel, thyroid function tests, inflammatory markers, glucose metabolism indicators, vitamin levels (particularly D, B12, and folate), and when indicated, hormone panels.

Disorders and/or should be further evaluated. Deficiencies should be corrected prior to consideration of HBOT.

5.5 Symptoms questionnaires

Symptom measurement should utilize the British Columbia Post-Concussion Symptom Inventory (BC-PSI) (45) as the core assessment, providing a validated 16-item scale specifically designed to align with ICD-10 diagnostic criteria for PCS. This instrument offers comprehensive coverage of cognitive, somatic, and emotional domains while demonstrating high test-retest reliability ($r=0.89$) and internal consistency ($\alpha=0.91$).

To ensure comprehensive assessment, the BC-PSI should be supplemented by:

1. Post-Concussion Symptom Scale (PCSS) - A 22-item scale embedded within the Sport Concussion Assessment Tool (SCAT), offering sensitivity to subtle symptom changes and established normative data across diverse populations. The PCSS provides valuable insights into symptom severity through its 0-6 rating scale (46).
2. Neurobehavioral Symptom Inventory (NSI) - A 22-item military-validated measure offering particular sensitivity to vestibular, cognitive, and emotional symptoms, with established minimally clinically important differences (MCIDs) to determine treatment response.

For domain-specific assessment, validated instruments should target prominent symptom clusters:

- Headache: The Headache Impact Test-6 (HIT-6) and Migraine Disability Assessment (MIDAS) provide functional impact measures, while headache diaries track frequency, intensity, and pattern changes (47).
- Sleep disturbance: The Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI) offer comprehensive sleep quality assessment (48).
- Vestibular/balance issues: The Dizziness Handicap Inventory (DHI) and Balance Error Scoring System (BESS) provide standardized functional measures (49, 50).
- Fatigue: The Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS) capture both intensity and functional impact of fatigue (51).

This multi-modal assessment approach facilitates comprehensive symptom characterization while enabling reliable tracking of treatment response across specific symptom domains, addressing the heterogeneous presentation typical in PCS.

5.6 Core Assessment Requirements:

- British Columbia Post-Concussion Inventory (BC-PSI): Clinically significant score ≥20 total
- Post-Concussion Symptom Scale (PCSS): Clinically significant score ≥21 total
    - 10-point change represents clinically meaningful difference
- Neurobehavioral Symptom Inventory (NSI): Clinically significant score ≥24 total
    - Minimally clinically important difference (MCID): 7-point reduction

5.7 Psychosocial Evaluation

The psychosocial evaluation should be performed by a trained neuropsychologist through a structured interview assessing pre-injury psychological functioning, current psychological symptoms, coping strategies, impact of symptoms on psychosocial functioning, family dynamics, support systems, and occupational and financial factors.

Standardized assessments should include:

1. **Short Form-36 Health Survey (SF-36)**: A comprehensive 36-item questionnaire measuring eight health domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. This provides a holistic view of health-related quality of life and functional status, allowing for comparison to population norms and tracking changes over time (52).

2. **(48)Pittsburgh Sleep Quality Index (PSQI)**: A 19-item self-report measure assessing sleep quality and disturbances over a one-month interval. It evaluates seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Sleep disturbances are common in TBI and can significantly impact recovery and daily functioning.

3. **Beck Depression Inventory-II (BDI-II)**: A 21-item self-report inventory measuring the severity of depression symptoms according to DSM criteria. It assesses cognitive, affective, and somatic symptoms of depression, which frequently co-occur with TBI and can complicate both diagnosis and treatment. Scores above 20 indicate moderate depression requiring further evaluation (53).

4. **Patient Health Questionnaire-9 (PHQ-9)**: A 9-item self-report screening tool designed to detect and measure the severity of depression based on DSM criteria. It evaluates key symptoms including mood, sleep disturbances, energy levels, concentration, appetite changes, and thoughts of self-harm, which may overlap with post-TBI symptoms and affect recovery outcomes. Scores of 10 or higher suggest moderate depression warranting clinical attention, while scores of 15 or above indicate moderately severe depression requiring intervention (54).

5. **Generalized Anxiety Disorder-7 (GAD-7)**: A 7-item tool screening for and assessing the severity of generalized anxiety disorder. It measures frequency of anxiety symptoms over the past two weeks, with scores of 10 or greater indicating moderate anxiety. Anxiety symptoms often accompany TBI and can exacerbate cognitive difficulties and functional impairment (55).

6. **Brief Symptom Inventory-18 (BSI-18)**: An 18-item screening tool for psychological distress across three dimensions: somatization, depression, and anxiety. It provides a Global Severity Index useful for tracking overall psychological distress over time. This measure can help identify psychological symptoms that may require additional intervention beyond HBOT (56).

7. **PTSD Checklist-Military Version (PCL-M) or PTSD Checklist-Civilian Version (PCL-C)**: These 17-item self-report measures assess symptoms of PTSD, with the PCL-M specifically addressing trauma related to military experiences and the PCL-C addressing civilian trauma. Both versions map to DSM-IV criteria for PTSD and help identify clinically significant symptoms that may affect treatment response. For military or veteran populations, the PCL-M should be used; for civilians, the PCL-C is appropriate (57).

8. **Clinician-Administered PTSD Scale for DSM-5 (CAPS-V)**: When PTSD is suspected based on elevated PCL-M or PCL-C scores (typically ≥33 for PCL-M in veterans or ≥30 for PCL-C in civilians), this structured clinical interview should be conducted. The CAPS-V is considered the gold standard for PTSD assessment, providing detailed evaluation of symptom frequency and intensity, functional impairment, and differential diagnosis considerations. It requires approximately 45-60 minutes to administer but provides essential information for treatment planning (58).

9. **Substance Use Screening Tools**: These should include the Alcohol Use Disorders Identification Test (AUDIT) for alcohol use patterns and the Drug Abuse Screening Test (DAST-10) for other substance use. Both brief screening tools help identify patterns of substance use that could affect treatment outcomes or indicate the need for concurrent substance use treatment (59, 60).

10. **Resilience Scale for Adults (RSA)**: A 33-item measure assessing six factors of resilience: perception of self, planned future, social competence, structured style, family cohesion, and social resources. Resilience factors can significantly moderate treatment outcomes and provide insight into supportive resources that may enhance recovery (61).

11. **Pain Catastrophizing Scale (PCS)**: A 13-item measure assessing catastrophic thinking related to pain experiences across three domains: rumination, magnification, and helplessness. Post-TBI headache and pain are common, and catastrophic thinking about pain can significantly impact treatment participation and outcomes (62).

Social support evaluation should assess family support networks, community resources, workplace accommodations, access to transportation for treatment, financial resources for the treatment period, and caregiver availability if needed. Psychological exclusion criteria include major depression with active suicidal ideation, severe untreated anxiety disorders, significant PTSD as a primary diagnosis, active substance use disorders, severe personality disorders affecting treatment adherence, poorly controlled psychotic disorders, and severe somatization disorder.

The assessment should also evaluate psychological readiness, including motivation for treatment, acceptance of injury and limitations, realistic treatment expectations, willingness to engage in concurrent therapies, and previous adherence to treatment regimens.

Exclusion Thresholds:

- BDI-II scores above 20 (moderate depression) require further evaluation
- GAD-7 scores ≥10 (moderate anxiety) require additional assessment
- Active suicidal ideation requires psychiatric stabilization before treatment
- Active substance use disorders require treatment before HBOT consideration
- AUDIT score ≥16 requires substance treatment prior to HBOT
- DAST-10 score ≥3 requires further assessment

5.8 Cognitive Evaluation

Cognitive evaluation should be performed by a trained neuropsychologist using objective computerized cognitive tests with high test-retest reliability. The following assessment tools are recommended based on their psychometric properties and

sensitivity to TBI-related cognitive deficits - at least one of those tools should be used for baseline and post-treatment evaluations:

1. **NeuroTrax (Mindstreams)** (63)
    - **Description**: A comprehensive computerized cognitive assessment system designed specifically for detecting mild impairment. It evaluates multiple cognitive domains including memory, executive function, attention, information processing speed, visuospatial skills, verbal function, and motor skills.
    - **Administration**: 45-60 minutes for the full battery; shorter customized batteries available.
    - **Alternate Forms**: Contains multiple equivalent alternate forms generated algorithmically, making it particularly suitable for repeated assessments with minimal practice effects.
    - **Test-Retest Reliability**: Excellent reliability coefficients ranging from 0.79 to 0.95 across domains. Global Cognitive Score shows 0.84 test-retest reliability at 6-month intervals.
    - **Validity for TBI**: Validated in mild to moderate TBI populations with demonstrated sensitivity to subtle cognitive changes following intervention.
    - **Scoring**: Provides standardized scores (mean=100, SD=15) for each cognitive domain and a Global Cognitive Score, with automatic comparison to age/education-matched normative data.
    - **Advantages**: Automatic scoring reduces administration bias; web-based platform allows for consistent administration across sites; particular strength in executive function assessment.
2. **CNS Vital Signs** (64)
    - **Description**: A computerized neurocognitive assessment battery that evaluates multiple domains including verbal and visual memory,

processing speed, executive function, psychomotor speed, reaction time, complex attention, and cognitive flexibility.

- **Administration**: 30-40 minutes for the full battery.
- **Alternate Forms**: Features 12 alternate forms for repeated testing scenarios.
- **Test-Retest Reliability**: Reliability coefficients ranging from 0.65 to 0.87 across domains. Higher reliability (>0.80) for processing speed and psychomotor speed; moderate reliability (0.65-0.75) for memory domains.
- **Validity for TBI**: Validated sensitivity to cognitive impairment in mild TBI, with particular strength in detecting processing speed and reaction time deficits.
- **Scoring**: Provides standardized scores for each domain and a Neurocognition Index, with automatic comparison to age-matched norms.
- **Advantages**: Brief administration time; good sensitivity to mild cognitive impairment; robust measure of processing speed.

3. **Cambridge Neuropsychological Test Automated Battery (CANTAB)** (65)
    - **Description**: A tablet-based assessment system measuring visual memory, attention, executive function, processing speed, and social cognition through non-verbal, culturally neutral tests.
    - **Administration**: Variable depending on selected tests; comprehensive battery requires 60-90 minutes.
    - **Alternate Forms**: Utilizes multiple parallel versions for most tests, generated through algorithmic parameter variation.
    - **Test-Retest Reliability**: Reliability coefficients ranging from 0.70 to 0.90 across subtests. Particularly high reliability (>0.85) for executive function measures.

- **Validity for TBI**: Extensively validated in TBI research, with demonstrated sensitivity to frontal lobe dysfunction and executive impairment.
- **Scoring**: Provides z-scores and percentiles based on large normative databases stratified by age, gender, and education.
- **Advantages**: Minimal language requirements makes it suitable for diverse populations; strong theoretical grounding in cognitive neuroscience; exceptional spatial working memory assessment.

4. **NIH Toolbox Cognitive Battery** (66)
    - **Description**: A comprehensive set of neuropsychological measures developed by the National Institutes of Health to assess cognitive function across the lifespan (ages 3-85). Includes measures of executive function, attention, episodic memory, language, processing speed, and working memory.
    - **Administration**: 30-45 minutes for the full battery.
    - **Alternate Forms**: Limited alternate forms available for some subtests; relies more on statistical correction for practice effects.
    - **Test-Retest Reliability**: Reliability coefficients ranging from 0.73 to 0.90 across domains over 7-21 day intervals. Fluid Cognition Composite shows particularly high reliability (0.89).
    - **Validity for TBI**: Validated for sensitivity to cognitive impairment in TBI, though less extensively than some other batteries.
    - **Scoring**: Provides age-corrected standard scores, fully adjusted scores (correcting for age, education, gender, and race/ethnicity), and uncorrected scores.
    - **Advantages**: National normative sample with comprehensive demographic corrections; integration with other NIH Toolbox measures (emotional, sensory, motor); iPad-based administration.

5. **Test of Variables of Attention (TOVA)** (67)
    - **Description**: A continuous performance test specifically designed to assess attention and impulse control. It measures attention across four variables: response time, response time variability, commission errors (impulsivity), and omission errors (inattention).
    - **Administration**: 21.6 minutes.
    - **Alternate Forms**: Single form design intended for repeated use with minimal practice effects.
    - **Test-Retest Reliability**: Reliability coefficients ranging from 0.74 to 0.87 for the various measures over 1-3 month intervals.
    - **Validity for TBI**: Demonstrated sensitivity to attention deficits following TBI, particularly in sustained attention and response consistency.
    - **Scoring**: Provides standard scores for each variable and an Attention Comparison Score, with comparison to age- and gender-matched norms.
    - **Advantages**: Highly specific to attention; minimal language/cultural demands; particularly useful for detecting subtle attention deficits not captured by broader cognitive batteries.
6. **Automated Neuropsychological Assessment Metrics (ANAM)** (68)
    - **Description**: A computerized battery initially developed for military use, measuring processing speed, attention/concentration, working memory, spatial processing, cognitive efficiency, and short-term memory for visual designs.
    - **Administration**: 20-45 minutes depending on selected subtests.
    - **Alternate Forms**: Multiple equivalent forms available through algorithmic stimulus generation.

- **Test-Retest Reliability**: Reliability coefficients ranging from 0.67 to 0.88 across subtests at 30-day intervals. Throughput scores (combining speed and accuracy) show the highest reliability.
- **Validity for TBI**: Extensively validated in military TBI populations; particular sensitivity to deployment-related mild TBI.
- **Scoring**: Provides percentile rankings and standard scores with military and civilian normative comparisons.
- **Advantages**: Extensive validation in military populations; efficient administration time; particularly good for tracking recovery trajectories in sports and combat-related concussion.

The cognitive assessment should evaluate global cognitive function, memory (verbal, visual, and working), information processing speed, executive functions (planning, inhibition, cognitive flexibility), attention (sustained, divided, selective), visuospatial processing, language function, and social cognition. Patients with a decrease of 0.5 standard deviations or greater in one or more cognitive domains compared to age-matched norms meet the cognitive deficit criterion for HBOT eligibility. Priority should be given to patients with deficits in multiple domains, and those with progressively worsening scores on serial testing warrant special consideration.

Test Selection Considerations:

- For patients with multiple previous assessments, prioritize tests with the strongest alternate forms (NeuroTrax, CANTAB) to minimize practice effects.
- For longitudinal monitoring, select tests with the highest test-retest reliability in domains most relevant to the patient's deficits.
- For military or veteran populations, ANAM may provide the most relevant normative comparisons.
- For patients with limited language proficiency, CANTAB provides the most culturally neutral assessment.

- For comprehensive assessment of attentional deficits, combine the TOVA with domain-specific measures from other batteries.

For complex cases, traditional neuropsychological testing may be added, along with functional cognitive assessments, ecological validity measures, assessment of cognitive fatigue and endurance, and evaluation of cognitive strategy use and compensation. The assessment should establish baselines for outcome measurement in primary cognitive domains most relevant to the individual's daily functioning, secondary domains showing subtle deficits, cognitive reserve estimation, and when available, comparison to pre-injury cognitive functioning.

Each assessment should use alternate forms when available to minimize practice effects, and statistical corrections for practice effects should be applied when interpreting results from repeated testing.

Cognitive Deficit Criterion:

- HBOT eligibility requires cognitive deficits ≥1.0 SD below age-matched norms in at least one domain

5.9 Physical Evaluation

Physical evaluation should be conducted by a trained physical therapist and thoroughly documented using standardized assessment forms, video recording for later comparison, and quantitative measurements.

Motor assessment should include manual muscle testing of all limbs, dynamometer-based strength measurements, fine motor coordination testing, gait analysis using quantitative parameters, range of motion measurements, motor fatigability assessment, and spasticity assessment when applicable.

Patients meet the motor deficit criterion if they demonstrate muscle power 2/5, 3/5, or 4/5 on any limb related to the injury, dynamometer values below age-appropriate norms, abnormal gait parameters on quantitative assessment, or fine motor skill deficits on standardized testing.

Balance assessment should utilize the Balance Error Scoring System (BESS) (69), Sensory Organization Test (SOT) (70), Functional Gait Assessment (FGA) (71),

Dynamic Gait Index (DGI) (72), computerized dynamic posturography, and Vestibular/Ocular Motor Screening (VOMS) (73). Balance deficit criteria are met when the BESS score falls below normal function for the patient's age group, SOT shows an abnormal composite score or failure of conditions 5 or 6, FGA score is below 22/30, or DGI score is below 19/24.

Cerebellar function assessment should include finger-to-nose testing, rapid alternating movements, heel-to-shin testing, tandem gait assessment, and standardized rating scales such as the International Cooperative Ataxia Rating Scale (ICARS) or Scale for the Assessment and Rating of Ataxia (SARA) (74). Any limb ataxia on neurological evaluation, SARA score above 3 points, or ICARS score above 5 points meets the cerebellar deficit criterion.

Speech and language assessment should employ the Western Aphasia Battery-Revised (WAB-R), Boston Diagnostic Aphasia Examination (BDAE), motor speech production evaluation, cognitive-linguistic assessment, and reading and written language assessment. The speech deficit criterion is met by any aphasia on standardized evaluation, dysarthria affecting intelligibility, anomia on confrontation naming tests, or reduced verbal fluency on timed tests.

Physical Deficit Criteria for HBOT Eligibility: At least ONE of the following must be present:

1. **Motor Deficit:**
    - Muscle power ≤4/5 on any limb related to the injury
    - Dynamometer values <85% of age-appropriate norms
    - Abnormal gait parameters on quantitative assessment
    - Fine motor skill deficits >1.5 SD below norms on standardized testing
2. **Balance Deficit:**
    - BESS score >10 total errors
    - SOT composite score <70 or failure of conditions 5-6
    - FGA score <22/30

- DGI score <19/24

3. **Cerebellar Deficit:**
    - Any limb ataxia on neurological evaluation
    - SARA score >3 points
    - ICARS score >5 points
4. **Speech Deficit:**
    - Any aphasia on standardized evaluation
    - Dysarthria affecting intelligibility (<90%)
    - Anomia on confrontation naming tests (<2 SD below norms)
    - Reduced verbal fluency on timed tests (<1.5 SD below norms)

5.10 Brain Imaging Evaluation

Comprehensive brain imaging is essential for eligibility determination, baseline documentation, and outcome assessment.

Anatomical imaging preferably uses high-resolution (3T) MRI with required sequences including T1-weighted 3D, T2-weighted, FLAIR, susceptibility weighted imaging (SWI), and diffusion-weighted imaging (DWI). Advanced sequences should include diffusion tensor imaging (DTI). CT should be used only if MRI is contraindicated.

Functional imaging options include brain SPECT with Tc-99m ECD tracer, with advanced options of dynamic susceptibility contrast (DSC) perfusion with cerebrovascular reactivity mapping and diffuse tracking imaging (DTI).

Quantitative analysis should include comparison to age-matched normative databases, region of interest analysis of Brodmann areas, voxel-based morphometry for structural analysis, tractography for white matter pathway assessment, network analysis using graph theoretical approaches, and automated lesion detection algorithms.

Functional/anatomical mismatch criteria for cognitive deficits require a decrease of -1 to -2.5 standard deviations in at least one relevant Brodmann area.

Note: Decreases of -3SD or lower suggest potential necrosis with poor treatment response.

Structural Imaging Thresholds:

- Microhemorrhages on SWI: ≥2 small punctate lesions
- White matter hyperintensities on FLAIR: Modified Fazekas scale ≥2

Diffusion Tensor Imaging Thresholds:

- Fractional Anisotropy (FA): Reduction of >2 SD in corpus callosum
- Mean Diffusivity (MD): Increase of >2 SD in affected white matter tracts
- FA reduction >10% in relevant white matter tracts

Functional Imaging Thresholds:

- SPECT: Regional cerebral blood flow reduction >1.5 SD compared to normative database
- DSC: >1.5 SD reduction from normal values

Cognitive-Imaging Correlations

For HBOT eligibility, there must be clear correspondence between:

- Memory Deficits: Must correlate with abnormal findings in:
    - Hippocampal regions (reduced perfusion on SPECT/PET by >1.5 SD)
    - Medial temporal lobes (BA 28, 34, 38) showing metabolic reduction
    - Fornix or hippocampal white matter tracts (FA reduction >10% on DTI)
- Executive Function Deficits: Must correlate with abnormal findings in:
    - Prefrontal cortex (BA 9, 10, 46) showing >1.5 SD reduced perfusion/metabolism
    - Dorsolateral prefrontal cortex activity reduction on fMRI during executive tasks

- Anterior cingulate (BA 24, 32) showing metabolic/perfusion changes

- Attention Deficits: Must correlate with abnormal findings in:
  - Anterior cingulate cortex (BA 24, 32) showing >1.5 SD reduction
  - Right frontal and parietal regions showing reduced perfusion
  - Superior longitudinal fasciculus showing DTI abnormalities (FA reduction >10%)
- Processing Speed Deficits: Must correlate with abnormal findings in:
  - Subcortical white matter showing DTI abnormalities
  - Widespread reduction in cerebral blood flow on ASL or SPECT
  - Corpus callosum integrity compromise on DTI (FA reduction >10%)

Physical-Imaging Correlations

For HBOT eligibility, there must be clear correspondence between:

- Motor Deficits: Must correlate with abnormal findings in:
  - Primary motor cortex (BA 4) showing >1.5 SD reduced perfusion/metabolism
  - Corticospinal tract showing reduced FA (>10%) on DTI
  - Basal ganglia structures showing functional or structural abnormalities
  - Supplementary motor area (BA 6) showing reduced activation on functional imaging
- Balance Deficits: Must correlate with abnormal findings in:
  - Vestibular nuclei pathways showing functional connectivity disruption
  - Cerebellar-vestibular pathways showing DTI abnormalities
  - Temporal-parietal junction showing metabolic reduction
  - Cerebellar vermis showing structural or functional abnormalities

- Cerebellar Deficits: Must correlate with abnormal findings in:
    - Cerebellar hemispheres showing >1.5 SD reduced perfusion/metabolism
    - Cerebro-cerebellar pathways showing reduced FA on DTI
    - Middle cerebellar peduncles showing structural or functional abnormalities
- Speech/Language Deficits: Must correlate with abnormal findings in:
    - Broca's area (BA 44, 45) for expressive deficits showing reduced activity
    - Wernicke's area (BA 22) for receptive deficits showing reduced metabolism
    - Arcuate fasciculus showing reduced FA (>10%) on DTI for language deficits
    - Left temporal-parietal regions showing hypoperfusion on functional imaging

5.11 Patient/Family Expectations Assessment

Thorough assessment of patient and family expectations is critical to successful outcomes. The evaluation should distinguish between realistic expectations (improvement in some but not all symptoms, gradual recovery requiring multiple sessions, need for continued rehabilitation efforts, variability in symptom improvement) and unrealistic expectations (complete symptom resolution, immediate improvements, permanent cure without ongoing management, equal improvement across all deficit areas).

Patient education should include review of evidence-based outcomes, explanation of neuroplasticity principles, discussion of individual prognosis based on assessment results, potential side effects and their management, timeline for expected improvements, role of concurrent therapies, and long-term management strategies.

Motivation assessment should evaluate readiness for commitment to the treatment schedule, willingness to engage in complementary therapies, ability to monitor and document symptoms, interest in active participation in recovery, and history of adherence to medical recommendations. Support system evaluation should examine family understanding of the treatment process, availability of transportation and logistical support, financial resources and insurance coverage, work/school accommodations during treatment, and long-term support for continued recovery.

Assessment methods include structured interviews with patients and families, expectations questionnaires, goal-setting exercises with realistic targets, review of previous treatment experiences, and rehabilitation readiness assessment. Exclusion criteria based on expectations include patients with persistently unrealistic expectations despite education, primary goal of disability documentation, unwillingness to participate in recommended concurrent therapies, inadequate support systems for treatment completion, or active litigation where treatment outcome may influence legal proceedings.

A formal expectations contract detailing agreed-upon goals, potential benefits, limitations, and commitments should be signed by the patient prior to treatment initiation.

6. Contraindications and Risk Assessment

Thorough risk assessment must be conducted before initiating HBOT to ensure patient safety.

Absolute Contraindications:

- Untreated pneumothorax: Any radiographic evidence
- History of spontaneous pneumothorax without surgical intervention
- Skull deformities
- Current treatment with doxorubicin, bleomycin, disulfiram, or cisplatin
- Unrepaired tympanic membrane perforation
- Unhealed large skull fractures or defects (e.g., craniectomy)

- Pregnancy
- Severe untreated claustrophobia
- High-grade fever (>101.5°F/38.5°C) or active infection
- Seizure disorder not controlled with medication (any seizure within past 30 days)
- Severe COPD with CO2 retention (PCO2 >50 mmHg)

Relative Contraindications Requiring Evaluation:

- Upper respiratory infection or sinusitis
- History of thoracic surgery
- Uncontrolled hypertension (>180/110 mmHg)
- Heart failure with EF < 30%
- Pregnancy in second or third trimester
- History of seizure disorder controlled with medication
- Emphysema with bullae
- Previous spontaneous pneumothorax with surgical repair
- Asthma requiring frequent medication
- Implanted devices with pressure limitations
- Previous chest or ear surgery
- Congenital spherocytosis
- Optic neuritis

6.1 Special considerations for TBI patients:

- Patients with increased risk of seizures in patients with previous post-traumatic seizures, potential for temporary symptom exacerbation during the initial treatment phase, necessary medication adjustments during the treatment course, enhanced sensitivity to oxygen toxicity in patients with certain genetic

polymorphisms, altered physiological responses in patients with autonomic dysfunction, impaired ability to equalize ear pressure in patients with cognitive deficits, challenges with anxiety management for patients with PTSD comorbidity, and potential drug-HBOT interactions with psychotropic medications.

- Patients without a stable support system – Due to the demanding nature of the treatment schedule and potential symptom fluctuations, a strong support system is essential. In some cases, a residential treatment facility may be necessary to ensure safety and treatment adherence.
- Patients with severe psychiatric comorbidities – Individuals with severe psychiatric conditions unrelated to their TBI may experience exacerbation of those conditions during HBOT and should be evaluated carefully before initiation.
- Patients with limited cognitive reserves – For individuals with severe cognitive deficits who cannot understand or comply with treatment procedures, HBOT may present challenges requiring additional support measures.
- Patients with suicidal ideation – Individuals experiencing active suicidal thoughts require careful psychiatric evaluation before beginning HBOT. Appropriate psychiatric interventions and safety measures must be implemented prior to treatment initiation.

Risk management strategies should include individualized treatment protocol modifications based on risk factors, close monitoring during initial sessions, graduated pressurization protocols for at-risk patients, prophylactic treatments for common side effects, emergency protocols specific to the TBI population, medication adjustments prior to treatment initiation, pre-treatment anxiety management techniques, specialized ear equalization techniques, and seizure precautions for high-risk patients.

Comprehensive documentation should include a risk assessment form, informed consent detailing risks, benefits, and alternatives, clearance documentation from specialists when indicated, medication reconciliation form, emergency contact information, procedures for managing medical emergencies, and protocols for reporting and managing adverse events. A standardized risk assessment tool specific to HBOT in

TBI patients should be utilized to quantify individual risk and guide protocol modifications.

Exclusion Criteria Based on Expectations:

- Persistently unrealistic expectations despite education
- Primary goal of disability documentation
- Unwillingness to participate in recommended concurrent therapies
- Inadequate support systems for treatment completion
- Active litigation where treatment outcome may influence legal proceedings

Required Documentation:

- Formal expectations contract detailing agreed-upon goals, potential benefits, limitations, and commitments

7. Pre-Treatment Evaluation and Preparation

7.1 Smoking Cessation

Concerns have been raised regarding the effect of HBOT on pulmonary function. To minimize potential risks, smokers should be encouraged to quit smoking before starting HBOT. For many patients, quitting smoking has been a first step in their healing journey. Framing this success as a meaningful achievement can serve as a marker of the patient's commitment to recovery.

7.2 Adjustment of Medication Regimen

Certain medications may interfere with the neuroplasticity mechanisms of HBOT:

- **Benzodiazepines** depress multiple gene expressions in the brain, including neuroplasticity-related genes, and should be tapered if possible before starting HBOT. In some cases, severe insomnia or anxiety may accompany benzodiazepine cessation, requiring careful consideration of risks and benefits.
- **Anticonvulsants** are often necessary for post-traumatic seizure management and generally should not be discontinued, but doses should be optimized and stabilized before treatment.

- **Psychotropic medications** should be adjusted and stabilized before HBOT, as treatment-related symptom fluctuations may complicate the assessment of medication effects and make it difficult to evaluate the impact of HBOT.

7.3 Pre-Treatment analysis

Following the completion of the evaluations, an integration meeting with the clinical team should be conducted. The purpose is to review the patient's symptoms, cognitive assessment results, and brain imaging to integrate this information for a comprehensive understanding of the baseline condition.

The team will review the results with the patient and explain about potential effects that may arise during treatment, including possible temporary cognitive fluctuations and symptom exacerbation.

The comprehensive treatment program should be reviewed, emphasizing the role of each supportive therapy provided as part of the overall care plan.

8. Treatment Protocol

8.1 Standard Regimen

The standard HBOT protocol for TBI patients includes session parameters of 2.0 atmospheres absolute (ATA) pressure, 100% oxygen, with 5-minute air breaks every 20 minutes of oxygen exposure. Each session should provide 90 minutes of total oxygen time with a total session duration of approximately 120 minutes including compression and decompression phases. Compression and decompression rates should be set at 0.1 ATA per minute or adjusted to the patient's comfort level.

The treatment schedule consists of a basic protocol of 40 daily sessions, 5 days per week over 8 weeks (not more than 1 session per day). For many patients, an extended protocol of 60 sessions over 12 weeks is recommended based on recent evidence showing enhanced outcomes with longer treatment courses. Complex cases may benefit from an advanced protocol of 80 sessions over 16 weeks. Weekend breaks are standard unless clinical needs dictate otherwise, and session timing should be consistent when possible to maintain physiological adaptation.

The treatment process can be divided into distinct phases. The initiation phase (sessions 1-10) focuses on gradual acclimation to the chamber environment, comfort and anxiety management, establishment of proper ear equalization techniques, close monitoring for adverse effects, and baseline symptom tracking. The early treatment phase (sessions 11-30) introduces concurrent therapies when appropriate, maintains vigilance for temporary symptom fluctuations, adjusts treatment parameters if needed, and includes regular physician review of progress. The late treatment phase (sessions 31-60) intensifies concurrent rehabilitative therapies, continues monitoring for clinical response, and begins preparation for post-treatment maintenance.

8.2 Facility and staff

HBOT can be administered in either multiplace or monoplace chambers. Multiplace chambers accommodate multiple patients simultaneously, breathing oxygen through masks and allowing medical staff to be present during treatment. Monoplace chambers are compact, single-patient units typically pressurized with pure oxygen.

For TBI patients with cognitive, emotional, or behavioral challenges, treatment in a multiplace facility is recommended. Having medical staff with expertise in neurological rehabilitation present in the chamber during sessions ensures that anxiety, confusion, disorientation, or physical discomforts are effectively managed, promoting adherence to the treatment course.

Staff should be educated in TBI-informed care to engage positively with this population, fostering a safe and supportive environment. This includes understanding cognitive fatigue, executive function deficits, memory issues, emotional lability, and other common TBI sequelae.

8.3 Treatment Monitoring and Adjustments

Regular monitoring during the HBOT course is essential for optimizing outcomes. Patients should be evaluated by the treating physician every 3-4 weeks, with more frequent assessments if clinical status changes. Symptomatic worsening can be expected during the first 15-30 sessions and should not necessarily lead to treatment discontinuation unless severe or persistent. A formal clinical evaluation by the physician after 30-40 sessions serves as a critical checkpoint regarding patient response.

In cases of significant symptomatic worsening reported by the patient after 30-40 sessions, an in-depth evaluation is needed. Self-reported questionnaires can complement the physician's interview, though it should be noted that currently, no objective biomarker (EEG, eye tracker, etc.) has proven valid for interim response evaluation.

Protocol adjustments may be necessary based on individual patient responses. Options include adjusting pressure (temporary reduction to 1.5 ATA) and implementing personalized pre-chamber protocols (such as hydration, ear management, or anxiety control measures).

9. Concurrent Therapies

Concurrent rehabilitative therapies can significantly enhance HBOT outcomes and should be integrated into the treatment plan. Physical therapy, speech therapy, and cognitive therapy can be performed immediately before or after each hyperbaric session to capitalize on the enhanced neuroplasticity window created by HBOT. Evidence suggests that rehabilitative therapies performed within 2-3 hours of HBOT may have synergistic effects on neural recovery.

9.1 Physical therapy

Physical therapy should focus on addressing specific motor deficits identified in the baseline assessment, with progressive challenge to facilitate functional improvements. Speech and language therapy should target specific communication deficits with evidence-based approaches tailored to the patient's profile. Cognitive rehabilitation should employ both restorative and compensatory approaches, utilizing computer-based training programs with demonstrated efficacy in TBI populations.

9.2 Cognitive Training During and Outside HBOT Sessions

In-Chamber Cognitive Training: Structured cognitive activities can be incorporated during HBOT sessions to maximize therapeutic time:

- Simple attention, memory, and processing speed exercises using waterproof materials or appropriately protected electronic devices

- Guided mental imagery involving visualization of motor skills or daily functional activities that activate relevant neural pathways
- Audio-guided cognitive exercises delivered via headphones, including attention tasks, language comprehension, or working memory training
- Progressive difficulty levels adjusted based on individual performance and tolerance
- Brief pre-session instruction and post-session performance review

The cognitive training protocol should be customized to:

- Account for the chamber environment (limited movement, supine position)
- Address specific cognitive deficits identified in baseline assessment
- Avoid excessive cognitive fatigue during pressurization phases
- Provide sufficient variety to maintain engagement over multiple sessions

Out-of-Chamber Cognitive Training: Between HBOT sessions, a structured cognitive training program should include:

- Computer-based cognitive rehabilitation platforms with demonstrated efficacy in TBI (e.g., BrainHQ, Cogmed)
- Consistent daily practice sessions of 20-30 minutes
- Tasks targeting specific deficit areas with progressive challenge
- Regular performance monitoring and protocol adjustments
- Transfer training to apply improved cognitive skills to daily activities
- Integration of metacognitive strategies for real-world application

For optimal neuroplasticity, cognitive training difficulty should be calibrated to maintain approximately 70-80% success rate, challenging the patient without creating excessive frustration. In-chamber and out-of-chamber cognitive exercises should be coordinated to create a complementary program rather than duplicate efforts.

Bi-weekly sessions with a neuropsychologist or cognitive rehabilitation specialist should be scheduled to:

- Monitor cognitive function
- Strengthen compensatory strategies
- Assess any cognitive fluctuations
- Provide cognitive exercises tailored to deficit areas
- Adjust cognitive training programs based on progress

Psychoeducation is an essential treatment tool, providing a biological rationale for the cognitive and emotional changes that occur during treatment.

9.3 Psychological Support

Many TBI patients benefit from psychological interventions concurrent with HBOT:

Individual Support:

- Adjustment counseling to address emotional responses to injury and recovery
- Cognitive-behavioral therapy for managing depression, anxiety, or post-injury mood changes
- Coping skills development for symptom management and stress reduction
- Regular monitoring of psychological status throughout the HBOT course

PTSD Management: For patients with comorbid PTSD symptoms:

- Trauma-focused therapies modified for TBI-related cognitive limitations
- Careful coordination of trauma processing with HBOT schedule
- Enhanced monitoring for symptom exacerbation during treatment
- Specialized approaches such as Cognitive Processing Therapy adapted for TBI

Family Support:

- Education for family members about TBI, recovery expectations, and HBOT process

- Communication strategies for supporting the patient
- Guidance for managing behavioral or personality changes
- Resources for caregiver stress management

Psychological interventions should be scheduled to avoid patient fatigue and maximize engagement, typically on non-HBOT days or with sufficient recovery time between sessions. Regular communication between mental health providers and the HBOT treatment team is essential for coordinated care.

9.4 Nutritional Support

Nutritional support during HBOT should emphasize antioxidant-rich foods, omega-3 fatty acids, and adequate hydration. Specific supplements that may support neural recovery include omega-3 fatty acids (2-3g daily), vitamin D (maintaining levels >30 ng/mL), magnesium (400-600mg daily), and antioxidants such as vitamin E, vitamin C, and alpha-lipoic acid, though these should be taken several hours apart from HBOT sessions.

9.5 Sleep and Stress Management

Sleep optimization strategies are critical for many TBI patients and should include cognitive-behavioral therapy for insomnia, sleep hygiene education, and when necessary, careful pharmacological management. Stress reduction techniques such as mindfulness meditation, biofeedback, and breathing exercises can complement HBOT and help manage common TBI-related symptoms.

9.6 Medical Monitoring

Changes in medication regimens are not recommended during the treatment course, as they may complicate the identification of HBOT's effects on cognition and function. Regular medical monitoring should include:

- Bi-weekly meeting with a physician
- Daily vital sign checks
- Monitoring for potential side effects (ear pain, vision changes, fatigue)

- Adjustment of supportive measures as needed
- Assessment of cognitive and physical function trends

10. Special Considerations

10.1 Pediatric Patients

Treatment of pediatric TBI patients (under 18 years) requires specific modifications. Evaluation protocols should incorporate age-appropriate assessment tools, with particular attention to developmental stage and educational impact of symptoms. Neuroimaging interpretation must account for developmental changes in brain structure and function.

Treatment protocols typically employ slightly lower pressures (1.5 ATA) for patients under 14 years of age, with shorter session durations (45-60 minutes of oxygen) and careful monitoring for behavioral signs of oxygen toxicity which may manifest differently than in adults. The chamber environment should be adapted for pediatric comfort with appropriate distraction techniques, and parent/guardian presence in the chamber may be beneficial for younger children.

Outcome assessment must incorporate school performance metrics, age-appropriate functional measures, and parental/teacher observations. Long-term follow-up is particularly important given the developing brain's ongoing maturation.

10.2 Geriatric Patients

Geriatric patients (over 65 years) present unique challenges and considerations for HBOT treatment. Comprehensive pre-treatment evaluation must include careful assessment of comorbidities, with particular attention to cardiovascular and pulmonary status. Medication review is critically important due to the high prevalence of polypharmacy in this population.

Treatment protocols for geriatric patients often benefit from a more gradual initiation phase with slower compression rates and potentially lower initial pressures (1.5 ATA) for the first 5-10 sessions. Session frequency may be reduced to 3-4 times weekly if

fatigue becomes a limiting factor. Close monitoring of ear equalization is essential, as presbycusis and reduced tympanic membrane mobility may increase barotrauma risk.

Special attention should be paid to cognitive assessment in this population, with careful distinction between TBI-related cognitive changes and those associated with normal aging or early neurodegenerative processes. Follow-up should include close monitoring for functional independence and quality of life improvements, which may be more clinically relevant than absolute cognitive test scores in this population.

10.3 Patients with Comorbidities

The presence of comorbid conditions requires specialized approaches to HBOT for TBI. Patients with post-traumatic stress disorder (PTSD) that co-occurs with TBI may still benefit from HBOT, particularly when the PTSD is not the dominant clinical feature. Treatment should incorporate appropriate psychological support, and chamber protocols may need modification to accommodate anxiety triggers. Recent studies have shown that HBOT can actually improve PTSD symptoms when they co-occur with TBI-related brain dysfunction.

For patients with seizure disorders, consultation with neurology is mandatory prior to treatment. Anticonvulsant medication levels should be optimized and maintained throughout the treatment course.

11. Implementation and Resource Requirements

The successful implementation of an HBOT program for TBI patients requires specific resources, personnel, and infrastructure. The physical facility should include multiplace hyperbaric chambers (preferred) or monoplace chambers with appropriate emergency access. Treatment areas should have dedicated space for patient assessment, chamber operations, and emergency response with specialized equipment for neurological emergencies.

A qualified multidisciplinary team is essential, including physicians, specially trained nursing staff, certified hyperbaric technologists, respiratory therapists,

neuropsychologists, physical therapists, occupational therapists, speech-language pathologists, and administrative support staff. Regular team meetings to review patient progress and coordinate care across disciplines significantly enhance outcomes.

Quality assurance processes should encompass regular equipment maintenance and testing, protocol adherence monitoring, adverse event tracking and analysis, treatment outcome measurement, and patient satisfaction assessment. A formal process for regular protocol review and update based on emerging evidence should be established.

12. Post-Treatment Evaluation and Follow-up

12.1 Post-Treatment evaluations

- **Functional brain imaging**: End-of-treatment analysis will enable comparison to pre-treatment functional imaging. Areas with significant changes will be noted.
- **Comprehensive cognitive assessment**: Post-treatment cognitive testing using the same instruments employed at baseline will document objective changes in function.
- **Comprehensive physical assessments**: Post-treatment cognitive testing using the same instruments employed at baseline will document objective changes in function.
- **Symptoms and quality of life evaluations**: A thorough assessment of subjective improvements using the validated questionnaires and tools.

12.2 Post-Treatment analysis

The meeting typically takes place 4 to 6 weeks after completion of the HBOT course, following completion of post-treatment evaluations. It should include:

- The patient's subjective assessment of treatment effects
- Review of changes in cognitive and physical function

- Discussion of functional brain imaging results, highlighting areas of improved perfusion or metabolism
- Integration of observed changes in symptoms with alterations in brain activity
- Development of a long-term management plan

Patients should be informed that the beneficial effects of treatment may continue to develop for several months after completion. Therefore, a re-evaluation three months after treatment completion is advisable.

12.3 Indications for Additional HBOT Sessions

Additional HBOT sessions should not be initiated immediately after completing the initial treatment course. This is because neuroplasticity-driven improvements often continue for up to three months post-treatment, reflecting the sustained biological processes activated during HBOT.

A repeated course of 20-40 sessions may be considered in the following cases:

- When significant progress was achieved during the initial HBOT course, but further improvement is still needed
- When initial symptom improvement was observed but later diminished over the course of several months or years

The decision to initiate a second HBOT course should be made collaboratively, involving the patient's rehabilitation physician and a hyperbaric physician with expertise in treating TBI.

12.4 Post-Treatment Follow-ups

Following the treatment course, as symptoms improve, it is important to address functional limitations. Patients should be gradually challenged to increase activity levels and participation, supported by structured plans for occupational and social reintegration.

Long-term follow-up should include:

- Scheduled assessments at 6, 12 and 24 months post-treatment

- Continuation of appropriate therapies at decreased frequency
- Home exercise and cognitive training programs
- Periodic re-evaluation of functional status
- Adjustment of strategies based on recovery trajectory
- Support for community reintegration and return to productive activities

Notably, even patients who made limited gains in rehabilitation before undergoing HBOT may find new opportunities for functional improvement as their neurological function improves.

13. Summary of TBI Diagnostic Criteria

TBI diagnosis requires:

1. **Documented Injury Event:**
    - Clear evidence of traumatic biomechanical forces to the head
    - May include impact, blast, or penetrating injury mechanisms
    - Medical documentation or reliable collateral history when records unavailable
2. **Post-Injury Symptoms:**
    - Development or worsening of symptoms following the TBI event that persist for more than 3 months.
    - Symptoms from at least three of the post-concussion syndrome clusters:
        - Physical symptoms (headache, dizziness, fatigue, sleep disturbance, etc.)
        - Cognitive symptoms (memory problems, difficulty concentrating, etc.)
        - Emotional and behavioral symptoms (irritability, anxiety, depression, etc.)
        - Autonomic and neuroendocrine symptoms (orthostatic intolerance, etc.)

3. **Objective Deficits:**
    - Cognitive deficits on standardized testing
    - Physical deficits (motor, balance, coordination, speech) on examination
    - Deficits consistent with expected consequences of the injury type
4. **Imaging Findings:**
    - Evidence of structural or functional abnormalities on appropriate brain imaging
    - Findings corresponding to clinical deficits
5. **Temporal Relationship:**
    - Onset of symptoms temporally related to injury
    - For chronic TBI (focus of these guidelines), persistence of symptoms beyond 3-6 months
6. **Exclusion of Alternative Explanations:**
    - Symptoms and deficits not better explained by other medical or psychiatric conditions
    - Comprehensive evaluation to rule out alternative diagnoses

12. Summary of HBOT Eligibility Criteria

For a patient to be eligible for HBOT treatment of TBI, ALL of the following criteria must be met:

1. **Documented TBI History:**
    - Confirmed traumatic brain injury (impact, blast, or penetrating)
    - Injury occurred at least 3-6 months prior to HBOT consideration
2. **Persistent Symptoms:**
    - Minimum of three symptoms from the post-concussion syndrome clusters
    - Symptoms causing functional impairment in daily activities
    - Symptoms persisting despite standard management approaches
    - Validated by standardized measures:
        - BC-PSI score ≥20, or
        - PCSS score ≥21, or

- NSI score ≥24

3. **Objective Cognitive Deficits:**
    - At least one cognitive domain ≥1.0 SD below age-matched norms
    - Documented by validated assessment tools
4. **Objective Physical Deficits:**
    - At least ONE of:
        - Motor deficit: Muscle power ≤4/5 or <85% of expected norms
        - Balance deficit: BESS >10 errors, SOT <70, FGA <22/30, or DGI <19/24
        - Cerebellar deficit: SARA >3 points or ICARS >5 points
        - Speech deficit: Any measurable aphasia or dysarthria affecting intelligibility
5. **Functional Brain Imaging Findings:**
    - Functional/anatomical mismatch on imaging
    - Regional abnormalities in brain regions corresponding to clinical deficits
    - Evidence of potentially recoverable tissue (penumbra) on functional imaging
    - Reduction of -1.0 to -2.5 standard deviations in relevant brain regions
6. **Strong Clinical-Imaging Correlation:**
    - Direct correspondence between specific deficits and regional brain abnormalities
    - Cognitive deficits correlating with abnormalities in corresponding brain regions
    - Physical deficits correlating with abnormalities in corresponding neural systems
    - Minimum correlation thresholds met (as detailed in section 8)
7. **Appropriate Patient Expectations:**
    - Realistic expectations for treatment outcomes
    - Motivation to participate in rehabilitation
    - Absence of significant psychological barriers to treatment
    - Adequate social support during treatment period

- Signed expectations contract

8. **Absence of Contraindications:**
    - No absolute contraindications
    - Relative contraindications evaluated and managed appropriately
    - Risk assessment completed with acceptable risk profile

These criteria should be applied comprehensively, recognizing that each patient presents with a unique pattern of symptoms, deficits, and psychosocial factors that influence eligibility. The strongest predictor of treatment success is the correlation between clinical deficits and imaging findings.

References

1. Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. The Lancet Neurology. 2017;16(12):987-1048.
2. Wilson L, Stewart W, Dams-O'Connor K, Diaz-Arrastia R, Horton L, Menon DK, et al. The chronic and evolving neurological consequences of traumatic brain injury. The Lancet Neurology. 2017;16(10):813-25.
3. Eve DJ, Steele MR, Sanberg PR, Borlongan CV. Hyperbaric oxygen therapy as a potential treatment for post-traumatic stress disorder associated with traumatic brain injury. Neuropsychiatr Dis Treat. 2016;12:2689-705.
4. Hadanny A, Efrati S. The Hyperoxic-Hypoxic Paradox. Biomolecules. 2020;10(6).
5. Meaney DF, Smith DH. Biomechanics of concussion. Clin Sports Med. 2011;30(1):19-31, vii.
6. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. Neurosurgery. 2014;75 Suppl 4(0 4):S24-33.
7. Vagnozzi R, Signoretti S, Cristofori L, Alessandrini F, Floris R, Isgro E, et al. Assessment of metabolic brain damage and recovery following mild traumatic brain injury: a multicentre, proton magnetic resonance spectroscopic study in concussed patients. Brain. 2010;133(11):3232-42.
8. Simon DW, McGeachy MJ, Bayir H, Clark RS, Loane DJ, Kochanek PM. The far-reaching scope of neuroinflammation after traumatic brain injury. Nat Rev Neurol. 2017;13(3):171-91.
9. Jassam YN, Izzy S, Whalen M, McGavern DB, El Khoury J. Neuroimmunology of Traumatic Brain Injury: Time for a Paradigm Shift. Neuron. 2017;95(6):1246-65.
10. Kenney K, Amyot F, Haber M, Pronger A, Bogoslovsky T, Moore C, et al. Cerebral Vascular Injury in Traumatic Brain Injury. Exp Neurol. 2016;275 Pt 3:353-66.
11. Ellis MJ, Ryner LN, Sobczyk O, Fierstra J, Mikulis DJ, Fisher JA, et al. Neuroimaging Assessment of Cerebrovascular Reactivity in Concussion: Current Concepts, Methodological Considerations, and Review of the Literature. Front Neurol. 2016;7:61.
12. Cheng G, Kong RH, Zhang LM, Zhang JN. Mitochondria in traumatic brain injury and mitochondrial-targeted multipotential therapeutic strategies. Br J Pharmacol. 2012;167(4):699-719.
13. Hayes JP, Logue MW, Sadeh N, Spielberg JM, Verfaellie M, Hayes SM, et al. Mild traumatic brain injury is associated with reduced cortical thickness in those at risk for Alzheimer's disease. Brain. 2017;140(3):813-25.
14. Vagnozzi R, Signoretti S, Tavazzi B, Floris R, Ludovici A, Marziali S, et al. Temporal window of metabolic brain vulnerability to concussion: a pilot 1H-magnetic resonance spectroscopic study in concussed athletes--part III. Neurosurgery. 2008;62(6):1286-95; discussion 95-6.
15. Nguyen R, Fiest KM, McChesney J, Kwon CS, Jette N, Frolkis AD, et al. The International Incidence of Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Can J Neurol Sci. 2016;43(6):774-85.
16. Nelson LD, Temkin NR, Dikmen S, Barber J, Giacino JT, Yuh E, et al. Recovery After Mild Traumatic Brain Injury in Patients Presenting to US Level I Trauma Centers: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Study. JAMA Neurol. 2019;76(9):1049-59.

17. McMahon P, Hricik A, Yue JK, Puccio AM, Inoue T, Lingsma HF, et al. Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. J Neurotrauma. 2014;31(1):26-33.
18. Efrati S, Ben-Jacob E. Reflections on the neurotherapeutic effects of hyperbaric oxygen. Expert Rev Neurother. 2014;14(3):233-6.
19. Thom SR. Oxidative stress is fundamental to hyperbaric oxygen therapy. J Appl Physiol (1985). 2009;106(3):988-95.
20. Rockswold SB, Rockswold GL, Zaun DA, Zhang X, Cerra CE, Bergman TA, et al. A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. J Neurosurg. 2010;112(5):1080-94.
21. Hadanny A, Rittblat M, Bitterman M, May-Raz I, Suzin G, Boussi-Gross R, et al. Hyperbaric oxygen therapy improves neurocognitive functions of post-stroke patients - a retrospective analysis. Restor Neurol Neurosci. 2020;38(1):93-107.
22. Yang Y, Wei H, Zhou X, Zhang F, Wang C. Hyperbaric oxygen promotes neural stem cell proliferation by activating vascular endothelial growth factor/extracellular signal-regulated kinase signaling after traumatic brain injury. Neuroreport. 2017;28(18):1232-8.
23. Tal S, Hadanny A, Sasson E, Suzin G, Efrati S. Hyperbaric Oxygen Therapy Can Induce Angiogenesis and Regeneration of Nerve Fibers in Traumatic Brain Injury Patients. Front Hum Neurosci. 2017;11:508.
24. Palzur E, Zaaroor M, Vlodavsky E, Milman F, Soustiel JF. Neuroprotective effect of hyperbaric oxygen therapy in brain injury is mediated by preservation of mitochondrial membrane properties. Brain Res. 2008;1221:126-33.
25. Hu Q, Manaenko A, Xu T, Guo Z, Tang J, Zhang JH. Hyperbaric oxygen therapy for traumatic brain injury: bench-to-bedside. Med Gas Res. 2016;6(2):102-10.
26. Hadanny A, Daniel-Kotovsky M, Suzin G, Boussi-Gross R, Catalogna M, Dagan K, et al. Cognitive enhancement of healthy older adults using hyperbaric oxygen: a randomized controlled trial. Aging (Albany NY). 2020;12(13):13740-61.
27. Yang YJ, Wang XL, Yu XH, Wang X, Xie M, Liu CT. Hyperbaric oxygen induces endogenous neural stem cells to proliferate and differentiate in hypoxic-ischemic brain damage in neonatal rats. Undersea Hyperb Med. 2008;35(2):113-29.
28. Tal S, Hadanny A, Berkovitz N, Sasson E, Ben-Jacob E, Efrati S. Hyperbaric oxygen may induce angiogenesis in patients suffering from prolonged post-concussion syndrome due to traumatic brain injury. Restor Neurol Neurosci. 2015;33(6):943-51.
29. Lin KC, Niu KC, Tsai KJ, Kuo JR, Wang LC, Chio CC, et al. Attenuating inflammation but stimulating both angiogenesis and neurogenesis using hyperbaric oxygen in rats with traumatic brain injury. J Trauma Acute Care Surg. 2012;72(3):650-9.
30. Chen X, Duan XS, Xu LJ, Zhao JJ, She ZF, Chen WW, et al. Interleukin-10 mediates the neuroprotection of hyperbaric oxygen therapy against traumatic brain injury in mice. Neuroscience. 2014;266:235-43.
31. Vlodavsky E, Palzur E, Soustiel JF. Hyperbaric oxygen therapy reduces neuroinflammation and expression of matrix metalloproteinase-9 in the rat model of traumatic brain injury. Neuropathol Appl Neurobiol. 2006;32(1):40-50.
32. Weaver LK, Howe S, Snow GL, Deru K. Arterial and pulmonary arterial hemodynamics and oxygen delivery/extraction in normal humans exposed to hyperbaric air and oxygen. J Appl Physiol (1985). 2009;107(1):336-45.

33. Hadanny A, Abbott S, Suzin G, Bechor Y, Efrati S. Effect of hyperbaric oxygen therapy on chronic neurocognitive deficits of post-traumatic brain injury patients: retrospective analysis. BMJ Open. 2018;8(9):e023387.
34. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury - randomized prospective trial. PLoS One. 2013;8(11):e79995.
35. Weaver LK, Wilson SH, Lindblad AS, Churchill S, Deru K, Price RC, et al. Hyperbaric oxygen for post-concussive symptoms in United States military service members: a randomized clinical trial. Undersea Hyperb Med. 2018;45(2):129-56.
36. Harch PG, Andrews SR, Rowe CJ, Lischka JR, Townsend MH, Yu Q, et al. Hyperbaric oxygen therapy for mild traumatic brain injury persistent postconcussion syndrome: a randomized controlled trial. Med Gas Res. 2020;10(1):8-20.
37. Hadanny A, Catalogna M, Yaniv S, Stolar O, Rothstein L, Shabi A, et al. Hyperbaric oxygen therapy in children with post-concussion syndrome improves cognitive and behavioral function: a randomized controlled trial. Sci Rep. 2022;12(1):15233.
38. Miller RS, Weaver LK, Bahraini N, Churchill S, Price RC, Skiba V, et al. Effects of hyperbaric oxygen on symptoms and quality of life among service members with persistent postconcussion symptoms: a randomized clinical trial. JAMA Intern Med. 2015;175(1):43-52.
39. Wolf G, Cifu D, Baugh L, Carne W, Profenna L. The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. J Neurotrauma. 2012;29(17):2606-12.
40. Cifu DX, Hart BB, West SL, Walker W, Carne W. The effect of hyperbaric oxygen on persistent postconcussion symptoms. J Head Trauma Rehabil. 2014;29(1):11-20.
41. Liu Z, Wang X, Wu Z, Yin G, Chu H, Zhao P. HBOT has a better cognitive outcome than NBH for patients with mild traumatic brain injury: A randomized controlled clinical trial. Medicine (Baltimore). 2023;102(37):e35215.
42. Ablin JN, Lang E, Catalogna M, Aloush V, Hadanny A, Doenyas-Barak K, et al. Hyperbaric oxygen therapy compared to pharmacological intervention in fibromyalgia patients following traumatic brain injury: A randomized, controlled trial. PLoS One. 2023;18(3):e0282406.
43. Weaver LK, Ziemnik R, Deru K, Russo AA. A double-blind randomized trial of hyperbaric oxygen for persistent symptoms after brain injury. Sci Rep. 2025;15(1):6885.
44. Harch PG, Andrews SR, Fogarty EF, Amen D, Pezzullo JC, Lucarini J, et al. A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. J Neurotrauma. 2012;29(1):168-85.
45. Iverson GL, Lange RT. Examination of "postconcussion-like" symptoms in a healthy sample. Appl Neuropsychol. 2003;10(3):137-44.
46. Echemendia RJ, Meeuwisse W, McCrory P, Davis GA, Putukian M, Leddy J, et al. The Sport Concussion Assessment Tool 5th Edition (SCAT5): Background and rationale. Br J Sports Med. 2017;51(11):848-50.
47. Shin HE, Park JW, Kim YI, Lee KS. Headache Impact Test-6 (HIT-6) scores for migraine patients: Their relation to disability as measured from a headache diary. J Clin Neurol. 2008;4(4):158-63.

48. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.
49. Alghwiri AA, Whitney SL, Baker CE, Sparto PJ, Marchetti GF, Rogers JC, et al. The development and validation of the vestibular activities and participation measure. Arch Phys Med Rehabil. 2012;93(10):1822-31.
50. Planchet J, Lynch CR, Mozzer PL, Seichepine D. Reliability of the Balance Error Scoring System test is maintained during remote administration. Concussion. 2023;8(2):CNC102.
51. Ziino C, Ponsford J. Measurement and prediction of subjective fatigue following traumatic brain injury. J Int Neuropsychol Soc. 2005;11(4):416-25.
52. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32(1):40-66.
53. Wang YP, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. Braz J Psychiatry. 2013;35(4):416-31.
54. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13.
55. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-7.
56. Petrowski K, Schmalbach B, Jagla M, Franke GH, Brahler E. Norm values and psychometric properties of the brief symptom inventory-18 regarding individuals between the ages of 60 and 95. BMC Med Res Methodol. 2018;18(1):164.
57. Wilkins KC, Lang AJ, Norman SB. Synthesis of the psychometric properties of the PTSD checklist (PCL) military, civilian, and specific versions. Depress Anxiety. 2011;28(7):596-606.
58. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychol Assess. 2018;30(3):383-95.
59. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction. 1993;88(6):791-804.
60. Shirinbayan P, Salavati M, Soleimani F, Saeedi A, Asghari-Jafarabadi M, Hemmati-Garakani S, et al. The Psychometric Properties of the Drug Abuse Screening Test. Addict Health. 2020;12(1):25-33.
61. Briganti G, Linkowski P. Item and domain network structures of the Resilience Scale for Adults in 675 university students. Epidemiol Psychiatr Sci. 2019;29:e33.
62. Hayashi K, Ikemoto T, Shiro Y, Arai YC, Marcuzzi A, Costa D, et al. A Systematic Review of the Variation in Pain Catastrophizing Scale Reference Scores Based on Language Version and Country in Patients with Chronic Primary (Non-specific) Pain. Pain Ther. 2022;11(3):753-69.
63. GM D. Guide to MindStreams Normative Data. 2012.
64. Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. Arch Clin Neuropsychol. 2006;21(7):623-43.

65. Zygouris S, Tsolaki M. Computerized cognitive testing for older adults: a review. Am J Alzheimers Dis Other Demen. 2015;30(1):13-28.
66. Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Slotkin J, et al. The cognition battery of the NIH toolbox for assessment of neurological and behavioral function: validation in an adult sample. J Int Neuropsychol Soc. 2014;20(6):567-78.
67. Rotem A, Danieli Y, Ben-Sheetrit J, Bashari A, Golubchik P, Ben-Hayun R, et al. Apparent lack of practice effects in the Test of Variables of Attention (TOVA) in adult ADHD. Atten Defic Hyperact Disord. 2019;11(1):73-81.
68. Vincent AS, Roebuck-Spencer TM, Cox-Fuenzalida LE, Block C, Scott JG, Kane R. Validation of ANAM for cognitive screening in a mixed clinical sample. Appl Neuropsychol Adult. 2018;25(4):366-75.
69. Bell DR, Guskiewicz KM, Clark MA, Padua DA. Systematic review of the balance error scoring system. Sports Health. 2011;3(3):287-95.
70. Broglio SP, Ferrara MS, Sopiarz K, Kelly MS. Reliable change of the sensory organization test. Clin J Sport Med. 2008;18(2):148-54.
71. Wrisley DM, Marchetti GF, Kuharsky DK, Whitney SL. Reliability, internal consistency, and validity of data obtained with the functional gait assessment. Phys Ther. 2004;84(10):906-18.
72. Herman T, Inbar-Borovsky N, Brozgol M, Giladi N, Hausdorff JM. The Dynamic Gait Index in healthy older adults: the role of stair climbing, fear of falling and gender. Gait Posture. 2009;29(2):237-41.
73. Mucha A, Collins MW, Elbin RJ, Furman JM, Troutman-Enseki C, DeWolf RM, et al. A Brief Vestibular/Ocular Motor Screening (VOMS) assessment to evaluate concussions: preliminary findings. Am J Sports Med. 2014;42(10):2479-86.
74. Schmitz-Hubsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology. 2006;66(11):1717-20.