



Hyperbaric oxygen therapy for Post-Traumatic Stress Disorder

Comprehensive Clinical Practice Guidelines

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Introduction

Post-traumatic stress disorder (PTSD) affects up to 30% of veterans returning from combat zones. Unfortunately, a significant proportion of these individuals do not respond to guideline-based treatments, leaving them with long-term social, behavioral, and occupational dysfunction(1-3). Accumulating evidence suggests that persistent PTSD symptoms are associated with alterations in brain activity and structure, particularly disruptions in the fronto-limbic circuitry(4). This highlights the importance of biologically based treatments aimed at repairing brain structures and restoring functional integrity.

In recent years, accumulating research has demonstrated that dedicated protocols of Hyperbaric Oxygen Therapy (HBOT) can induce neuroplasticity(5) and significantly improve clinical outcomes in conditions such as post-stroke, post-concussion syndrome, central sensitization disorders (e.g., fibromyalgia)(6-11), and most recently, PTSD. To induce neuroplasticity, HBOT protocols utilize repeated fluctuations in both pressure and oxygen levels(12). These fluctuations trigger a cascade of biological responses typically associated with hypoxia, without its related hazard, by leveraging a hyperoxygenated environment. This phenomenon is called the Hyperoxic-Hypoxic Paradox (HHP).

Recent clinical trials have demonstrated the benefits of HBOT for veterans suffering from treatment-resistant PTSD (13-23). By inducing neuroplasticity, HBOT has been shown to improve intrusive symptoms, avoidance behaviors, mood disturbances, cognitive function, and hyperarousal. The clinical improvements correlate with measurable enhancements in brain function and structural recovery.

However, HBOT is not a symptomatic treatment but rather a therapy aimed at addressing the core biological pathophysiology of PTSD. As a result, some patients may experience temporary symptom exacerbation during treatment, which, if not properly managed, could lead to treatment discontinuation. A particularly notable phenomenon observed in some patients during HBOT is the surfacing of previously inaccessible memories (24). While this process provides an opportunity for memory integration and resolution of intrusive symptoms, it can also provoke significant distress if not properly managed. Adequate support and guidance during treatment are essential to ensure a safe and effective HBOT course.

Improper management of the challenges, may have contributed to suboptimal outcomes observed in some clinical trials. As in these studies, worsening of symptoms led to premature treatment discontinuation limiting therapeutic effectiveness. Effectively addressing symptom fluctuations during HBOT is critical for optimizing therapeutic benefits for PTSD patients. A



structured approach that anticipates and manages these fluctuations can enhance patient adherence and significantly improve outcomes.

This document provides a comprehensive review of PTSD pathogenesis, with a particular emphasis on the biological effects of psychological trauma. It then presents preclinical and clinical data on the effects of HBOT on PTSD related symptoms, brain activity, and structural recovery. The second section of the document outlines clinical practice guidelines, offering detailed recommendations for patient selection, treatment protocols, symptom management, and follow-up care, ensuring a safe and effective HBOT treatment approach.

The clinical guidelines are based on data from clinical research studies (13, 15, 24, 25) pre-published data, and over eight years of clinical experience with hundreds of veterans treated at the Sagol Center for Hyperbaric Medicine and Research in Israel.

Part 1: Pathogenesis of PTSD and the effect of HBOT on PTSD.

Pathogenesis of PTSD

Acute exposure to a highly stress-inducing event initiates a pathophysiological cascade that can culminate in chronic cellular dysfunction. The immediate activation of the autonomic nervous system leads to alterations in blood perfusion, coupled with dysregulation of cortisol and catecholamine levels (26-28). These disruptions may induce cellular hypoxia, mitochondrial dysfunction, dendritic atrophy, and apoptosis, laying the foundation for long-term neurobiological consequences(29-32). Even long after the initial traumatic event has ended, persistent cellular damage, chronic mitochondrial dysfunction, and neuroinflammation may be observed (Fedida et al. in press).

At the tissue level, structural and functional alterations in the brain have been well documented (33).Neuroimaging studies consistently report changes in the prefrontal cortex and limbic system, which correlate with clinical symptoms and are associated with treatment resistance (31). Abnormalities in the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC), are strongly linked to deficits in cognitive control over emotional processing (34).Another hallmark of PTSD-related neuroimaging is abnormal hippocampal function, which plays a key role in memory integration and contextual processing. Notably, reduced hippocampal volume has been associated with lower responsiveness to certain treatments, further reinforcing the need for targeted biological interventions certain treatments (35).



The persistent nature of these neurobiological impairments and the correlation to treatment resistance underscores the potential therapeutic value of biologically based interventions that promote structural and functional recovery.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is a therapeutic intervention that utilizes controlled environmental changes, specifically alterations in pressure and gas concentrations to elicit targeted biological responses. Different HBOT protocols are designed to achieve specific physiological effects.

The administration of 100% oxygen at a pressure of 2 atmospheres absolute (ATA) increases arterial oxygen tension to approximately 1500 mmHg, with tissue oxygen levels reaching 200-400 mmHg(12). At these levels, the dissolved oxygen in the blood is sufficient to meet the body's total energy demands, even in areas with compromised perfusion. Oxygen delivery occurs via passive diffusion, bypassing vascular limitations, and fluctuations in oxygen levels are directly sensed by mitochondria, making them key mediators of HBOT's cellular effects(5).

The hyperoxic-hypoxic paradox (HHP) underlies HBOT's therapeutic efficacy with respects to induction of the regenerative cascade and neuroplasticity. Intermittent exposure to high oxygen levels triggers cellular pathways typically activated during hypoxia, particularly through the upregulation of hypoxia-inducible factors (HIFs). This paradoxical effect promotes angiogenesis, stem cells including neuronal stem cells proliferation, neurogenesis, mitochondrial biogenesis and migration, and cellular repair mechanisms without the detrimental effects of chronic oxygen extremes. Exposure to fluctuating oxygen levels is fundamentally different from chronic hyperoxia, which has detrimental effect.

Tissue Oxygenation: HBOT enhances tissue oxygenation, with sustained effects persisting for more than six hours post-session. This hyperoxic state optimizes aerobic metabolism, reduces lactate accumulation, and increases cerebral metabolic rates by enhancing dissolved oxygen content. By providing supraphysiological oxygen levels, HBOT addresses a fundamental energy crisis in malfunctioning brain tissue.

Mitochondrial function: At the cellular level, 80% of available oxygen is utilized by mitochondria. The low oxygen levels within mitochondria render them key oxygen sensors and critical signaling hubs. HBOT's effects on mitochondrial function and proliferation have been demonstrated in several studies. In a mice training model, HBOT facilitated mitochondrial oxidative and glycolytic capacities, increasing the expression of proteins involved in



mitochondrial biogenesis. Similar effects were observed in middle-aged athletes, where treatment increased mitochondrial mass and maximal oxygen phosphorylation capacity. Additional studies have highlighted the role of mitochondrial function in neuronal maintenance, particularly through mitochondrial transfer between astrocytes and neurons. Neurons release damaged mitochondria to astrocytes for degradation, while astrocytes provide functional mitochondria to neurons. HBOT facilitates these mechanisms, enhancing neuronal resilience against inflammatory insults and promoting recovery during the chronic delayed stage of various brain injuries.

HIF induction: HIF is a transcription factor that regulates cellular responses to oxygen availability. Under normoxic conditions, HIF undergoes degradation through hydroxylation, a process regulated by the balance between reactive oxygen species (ROS) and scavenging activity. During hyperoxia, increased oxygen availability enhances ROS production, but also boosts ROS scavenger levels, including glutathione peroxidase and superoxide dismutase. Upon returning to normoxia, scavenger levels remain elevated due to their longer half-life, leading to a low ROS/scavenging ratio. This mimics a hypoxic state, resulting in increased HIF expression due to suppressed HIF hydroxylation(36). The effect of repeated intermittent hyperoxia on HIF expression has been demonstrated across multiple animal models, organ systems, and cell types (37-39). HIF activation is neuroprotective, enhancing regenerative effects post-stroke and in spinal cord injuries. Moreover, HIF activation has been shown to directly enhance hippocampal function and memory performance.

Neuronal stem cell proliferation and neuroplasticity: HBOT has been shown to induce the proliferation and mobilization of hematopoietic and mesenchymal stem cells (40-43), as well as neuronal stem cells in the hippocampus and periventricular region(44-46). This effect contributes to neuroregeneration, as demonstrated in stroke, traumatic brain injury (TBI), and vascular dementia (42, 45, 47). Oxygen-dependent mechanisms also enhance white matter integrity. Studies have documented a significant increase in BDNF expression and upregulation of synapsin-1, accompanied by improvements in white matter integrity, as measured by diffusion tensor imaging (DTI) metrics.

Effect on inflammation: HBOT also demonstrates strong anti-inflammatory effects (48). Neuroinflammation is significantly reduced, as evidenced by decreased microglial activation and reduced astrogliosis, as demonstrated by lower Iba1 and GFAP expression. Pro-inflammatory cytokine activity is suppressed, and blood-brain barrier integrity is improved.



HBOT for PTSD

The effect of Hyperbaric Oxygen Therapy (HBOT) on post-traumatic response has been extensively studied in both preclinical and clinical settings. Preclinical studies using animal models of post-traumatic stress disorder (PTSD) have demonstrated the beneficial effects of HBOT on anxiety-related behaviours, as well as structural and functional changes in the brain (Fedida et al. in press and (49).

Early Clinical Evidence and Pilot Studies

Early clinical indications of HBOT's potential use in PTSD emerged from case reports, which described significant improvements in post-concussion syndrome (PCS) and post-traumatic symptoms following HBOT (50, 51). . These findings led to a series of pilot studies involving military personnel with PCS or traumatic brain injury (TBI), with cooccurring PTSD, demonstrating a reduction in post-traumatic symptoms following HBOT.

A pilot trial by Harch et al. al. (18) included 16 military personnel with prolonged PCS due to mild-to-moderate TBI or blast injury, 15 of whom were also diagnosed with PTSD. Participants underwent forty 60-minute HBOT sessions at 1.5 ATA, leading to a significant reduction in PTSD symptoms, as reflected by a decrease in the mean PTSD Checklist-Military (PCL-M) score from 67.4 ± 10.5 to 47.1 ± 16 ($P < 0.001$).

A single-center, double-blind, randomized, sham-controlled trial (22) conducted at the U.S. Air Force School of Aerospace Medicine compared 2.4 ATA HBOT to room air at 1.3 ATA, which was mistakenly regarded as a sham treatment, in 50 military personnel with TBI and PCS. Over an 8-week period, participants received 30 treatment sessions. PTSD symptoms were assessed using the PCL-M; however, the study did not specify how many participants met the diagnostic criteria for PTSD. Notably, both the 2.4 ATA and 1.3 ATA groups exhibited significant symptom improvement.

Cifu et al. al (16) conducted a double-blind study on 61 veterans with PCS, administering 40 sessions of 2 ATA HBOT with different oxygen concentrations (10%, 75%, or 100%). While PCS symptoms did not improve significantly, the PCL-M score decreased from 49.4 to 42.6 ($P < 0.05$) in the 2 ATA 100% oxygen group.

In a prospective case-control study, Harch et al. (10) examined 30 active service members or veterans with PCS, of whom 10 had PTSD symptoms. Following 40 HBOT sessions, PTSD symptoms significantly improved (PCL-M decreased from 63.4 ± 15.9 to 46.8 ± 16.5 , $P < 0.001$), with continued improvement at 6-month follow-up.



A retrospective study by Majayeni (52) evaluated 32 PCS patients with mild TBI, seven of whom had PTSD. Compared to those without PTSD, participants with PTSD demonstrated greater improvements in fatigue and mood scales ($P = 0.012$) and neurocognitive test scores ($P = 0.028$). A longer HBOT course was associated with greater benefits.

The BIMA trial (17) was a randomized, double-blind, sham-controlled study of 40 HBOT sessions at 1.5 ATA (100% oxygen) vs. 1.2 ATA (room air). Among 71 military personnel, 35 had PTSD. At 13 weeks, HBOT improved PTSD symptoms, sleep quality, anger control, and memory, with greater benefits in participants with PTSD compared to those with PCS alone.

Miller et al. (21) conducted a multicenter, double-blind, sham-controlled trial involving 72 veterans with PCS, randomized to three groups: 40 HBOT sessions at 1.5 ATA with 100% oxygen, 40 sessions at 1.2 ATA with room air or Standard care (no chamber exposure).

At baseline, 66% of participants met PTSD diagnostic criteria. Following treatment, PTSD symptoms improved in both active treatment arms, with mean reductions in PTSD Checklist scores of 11.4 (95% CI: 5.9–16.9) and 5.0 (95% CI: –1.7–11.6), respectively.

Challenges in Study Design

The Issue of Sham Controls: A persistent challenge in HBOT research is the adequacy of placebo control conditions. Many studies use mild hyperbaric exposure (e.g., 1.3 ATA or 1.2 ATA with room air) as a sham, but even slight increases in pressure and oxygen can exert physiological effects, making them low-dose active treatments rather than true placebos.

- Henry's Law dictates that increased atmospheric pressure enhances gas solubility in bodily tissues.
- Even at 1.05 ATA (such as at the Dead Sea, Israel, –436 meters below sea level), significant physiological effects have been documented effects (53–55).
- Among healthy volunteers, stem cell progenitor levels increased threefold after 10 sessions of 1.2 ATA with 21% oxygen oxygen (56) .

These findings suggest that improvements in sham groups in previous studies may underestimate HBOT's therapeutic potential. Several alternative placebo protocols have been proposed to address this limitation condition (57, 58) .

PCS vs. PTSD: Historically, most HBOT trials have recruited participants based on PCS rather than PTSD. Given the high comorbidity of PCS and PTSD (59, 60). Distinguishing HBOT's specific effects on PTSD has been challenging. Many symptoms, such as fatigue, irritability,



sleep disturbances, concentration difficulties, and emotional dysregulation, overlap between the two conditions.

PTSD-Specific HBOT Trial

In 2022, the first controlled study exclusively targeting veterans with treatment-resistant PTSD (without PCS) was published (14). Participants underwent sixty sessions of 2 ATA HBOT (100% oxygen, with air breaks every 20 minutes) over three months. Results showed that 71% of participants experienced symptom improvement, and 50% achieved remission. Functional MRI demonstrated improved brain activity, correlating with clinical response.

Long-term follow-up, conducted two years post-HBOT, revealed sustained improvements in PTSD symptoms, social and occupational function, and reduced medication use(15).

Recognizing the need for rigorous placebo control, a new placebo protocol was developed and validated in a 2021 study on veterans with treatment-resistant PTSD(13). This protocol involves initial compression to 1.2 ATA for the first 5 minutes to mimic pressure changes, followed by slow decompression to 1.02 ATA over 5 minutes, maintaining this level for the remainder of the session.

This biologically inactive placebo was incorporated into a randomized trial published in 2024, which confirmed significant PTSD symptom improvement in the HBOT group, while the placebo group showed no improvement(13). Brain connectivity also improved, further supporting HBOT's biologically driven therapeutic effect.

Both clinical studies utilized long treatment sessions to achieve effective and lasting therapeutic responses. Harch et al. recently published a review analyzing the total amount of oxygen delivered across PTSD studies, revealing a linear association between the cumulative "atmospheric minutes" (Ams) and treatment outcomes(61). Their findings suggest that a higher number of sessions and greater treatment pressure are associated with better clinical responses.

In conclusion, there is clear evidence supporting the efficacy of HBOT in alleviating post-traumatic symptoms in veterans who have not responded to first-line therapies. Given that different treatment protocols may yield varying outcomes, the evidence-based protocol of 60 daily sessions at 2 ATA, with 90 minutes of 100% oxygen and 5-minute air breaks every 20 minutes, should be recommended.

Adverse effects



HBOT is generally safe and well tolerated, with most side effects being mild and reversible (62).

Middle ear barotrauma is the most common side effect of hyperbaric treatment, with an incidence of approximately 2% (62), and a slightly higher frequency among individuals undergoing multiple treatments (63) (9). Sinus barotrauma is another common, reversible complication, typically occurring in patients with upper respiratory tract infections or allergic rhinitis (8).

Some patients may experience reversible myopia due to direct oxygen toxicity to the lens. While the exact etiology remains unclear, this condition typically resolves within days to weeks after completing treatment (62) (8).

Pulmonary barotrauma is an uncommon adverse effect, provided that pneumothorax has been ruled out before initiating HBOT (64). Other pulmonary complications, such as pulmonary edema, chest tightness, and cough, have been rarely reported in association with HBOT (65).

Seizures due to central nervous system (CNS) oxygen toxicity are a rare but notable complication of HBOT (12, 13). Patients receiving glucocorticoids, insulin, thyroid replacement therapy, or sympathomimetic medications may be at an increased risk for CNS oxygen toxicity.

HBOT has also been associated with hypoglycemia in some individuals with diabetes (14).

A retrospective analysis of 2,334 patients who underwent HBOT reported adverse events in 406 individuals (17.4%), with an overall incidence of 721 per 100,000 sessions (0.72%) (13). Subjective symptoms of barotrauma (sinus or ear pain) were reported in 79 individuals (3.4%), while 215 individuals (0.36%) had objective signs of middle ear barotrauma detected via otoscopy, and 16 individuals (0.02%) had objective sinus barotrauma. Only one case of HBOT-related seizure was reported.

A total of 58 individuals (2.5%) did not complete their prescribed HBOT sessions due to side effects, with middle ear barotrauma being the leading cause of treatment discontinuation (55%). Thus, HBOT is considered a relatively safe treatment, with reported adverse events being mild, self-limiting, and reversible in most cases.

Special concerns for PTSD treatment

Individuals with PTSD have often reported worsening of symptoms during the HBOT course. Harch et al. reported temporary worsening of emotional lability, depression, and headache in four of 16 recruited persons (18) (18). Miller et al. reported worsening claustrophobia in one



person (21). Among individuals who were recruited to a study on fibromyalgia related to child abuse- complex PTSD, symptoms worsened temporarily, at about the 20th session in most (66). As the HBOT course progressed, symptoms were resolved in all the patients. By the end of the HBOT treatment, clinical improvement was significant compared to baseline pre-HBOT assessments.

A unique phenomenon of memory recollection was first reported among persons with fibromyalgia (67). Similarly, recollection of inaccessible memories was reported in 35.7% of veterans with military-related PTSD (24). The memories surfaced mostly during the second month of the treatment; and their recollection was accompanied by temporary worsening of PTSD symptoms, and/or by somatic pain. Most of the reported resurfaced memories were related to traumatic events; nevertheless, it is important to note that changes in access to non-traumatic memories cannot be ruled out. While memory recollection and the accompanied distress may be considered adverse effects of the treatment, they may also represent an 'on target' effect that contributes to hippocampal-based memory processing in individuals with PTSD.

Part 2: Clinical Guidelines for HBOT in Veterans with PTSD

Criteria for HBOT Eligibility

Patients will be eligible for HBOT if they have a documented traumatogenic event with post-traumatic symptoms persistent for at least 3 months, have undergone at least one trial of trauma focused psychotherapy and suffer from moderate to severe symptoms as evaluated by PCL-5 or CAPS-V.

Contraindications for HBOT

- Untreated pneumothorax: Any radiographic evidence or a history of spontaneous pneumothorax without surgical intervention
- Current Smoking
- Pregnancy
- Active infection
- Seizure disorder not controlled with medication (any seizure within past 30 days)
- Severe COPD with CO₂ retention (PCO₂ >50 mmHg)
- Uncontrolled hypertension (>180/110 mmHg)



- Heart failure with EF < 30%
- Current psychosis or a history of recurrent psychotic episodes.

Patient Standard Evaluation Protocol

A thorough clinical evaluation should be conducted, including a detailed assessment of medical history, psychological history, medication regimen, and any history of drug or alcohol use.

The physical examination should include vital sign measurements, a pulmonary assessment, and an ENT evaluation, with particular attention to tympanic membrane integrity

Chest x-ray evaluation

A chest X-ray, performed within six months prior to first HBOT session, should be obtained to rule out pulmonary conditions that may contraindicate HBOT. Pulmonary function tests should be conducted for patients with a known history of respiratory disease.

Additional evaluations based on clinical history

Additional evaluations should be conducted based on the patient's medical history, including a cardiac assessment for those with cardiovascular disease, an ophthalmic examination for patients with a history of eye disease, blood glucose monitoring for diabetic patients, and a neurological assessment for individuals at risk of seizures.

Laboratory evaluation

Laboratory testing should include a complete blood count, glucose and HbA1c, electrolytes, renal function tests, liver enzymes, lipid profile, thyroid function tests, and vitamin levels (particularly vitamin D, B12, and folate), as well as an iron panel.

Any identified deficiencies should be corrected before initiating HBOT

Psychosocial Evaluation

A psychosocial evaluation should be conducted by a neuropsychologist with expertise in PTSD, using a structured interview to assess childhood trauma, current psychological symptoms, coping strategies, support systems, and occupational and financial factors.

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

For candidates currently undergoing psychotherapy, a confidentiality waiver should be completed, and the treating psychologist should be informed about the HBOT protocol, potential challenges, and strategies for effective treatment integration during HBOT.



Standardized assessments should include:

1. **Clinician-Administered PTSD Scale for DSM-5 (CAPS-V):** 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.
2. **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.

Brain Imaging Evaluation

Comprehensive brain imaging is recommended for baseline documentation, and outcome assessment, although no imaging based diagnosis is currently available.

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).

Functional imaging options include brain SPECT with Tc-99m ECD tracer or F-18 FDG-PET as primary modalities, with advanced options including resting-state functional MRI (rs-fMRI), arterial spin labeling (ASL) perfusion, dynamic susceptibility contrast (DSC) perfusion, cerebrovascular reactivity mapping, and task-based fMRI when appropriate.

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.



Pre-Treatment Evaluation, HBOT Regimen, Support, and Post-Treatment Management: comprehensive treatment Manual

General principles

- Patient selection and thorough preparation are crucial to ensure safety and efficacy.
- The treatment course is daily, extended and often subjectively demanding.
- Temporary worsening of symptoms is common.

The HBOT protocol is demanding, as it is based on daily sessions and can be associated with temporary symptom exacerbation. To ensure a safe and effective treatment experience, patient selection and thorough preparation are crucial. Patients should be well-informed about the expected effects of the treatment, including both the anticipated benefits and potential challenges that they may face along the way, such as alterations in sleep patterns, anxiety, changes in mood and energy levels, and of the potential surfacing of previously inaccessible memories.

Comprehensive patient education plays a key role in promoting adherence and compliance with the treatment regimen. Additionally, incorporating self-regulation techniques, practiced both before and during the course, can help patients manage symptom worsening and maintain emotional balance throughout the treatment process.

Population deserving special attention for which the treatment may be contraindicated:

- **Patients without a stable support system** – In some cases, a residential treatment facility may be necessary to ensure safety.
- **Patients with a history of psychosis unrelated to PTSD** – Due to theoretical risks, individuals with a history of psychosis, excluding those with transient drug-induced episodes, should be excluded from treatment.
- **Patients with limited experience in trauma-focused psychotherapy** – For individuals lacking prior exposure to psychotherapy-based trauma processing, the emergence of new memories may cause distress without the ability to effectively process them.
- **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.



Treatment protocol, facility and staff

- The protocol consists of sixty daily sessions, 5 days per week, with the pressure of 2ATA, 100% O₂ for 90 minutes with 5 minutes air brakes every 20 minutes.
- Multiplace, rather than monoplace chambers are suited for the treatment of patients with PTSD.
- Daily interactions with the center staff, both inside and outside the chamber, as well as with other patients, may be challenging but, when properly managed, can play an essential role in the success of the treatment.

The protocol used for the treatment of PTSD consists of 60 consecutive daily sessions, 5 days per week, with the pressure of 2ATA, 100% O₂ for 90 minutes with 5 minutes air brakes every 20 minutes. The protocol length and pressure provided were shown to have direct effect on its results (61).

Generally, HBOT can be administered in either multiplace or monoplace chambers. Multiplace chambers are designed to accommodate multiple patients simultaneously, breathing oxygen through oxygen masks and allowing medical staff to be present in chamber with the patients during treatment. Monoplace chambers are compact, single-patient units typically pressurized with pure oxygen. Based on the unique needs of post-traumatic patients who are prone for potential negative emotional experiences that may lead to treatment discontinuation - it is recommended that therapy be conducted in a multiplace facility. Having medical staff with expertise in PTSD present in the chamber during the entire session ensures that panic attacks and other acute distress responses or physical discomforts, are effectively managed, promoting adherence to the treatment course.

These multiple points of interaction help patients cope with difficulties, such as avoidance behaviors. Therefore, it is recommended to educate the staff so that trauma-informed personnel can engage positively with this post-traumatic population, fostering a safe and supportive environment.

Patients' selection

- HBOT should not be provided as first line treatment for PTSD.
- HBOT should be provided alongside with ongoing, psychotherapy.
- To ensure a continuum of care, the patient's therapist and the therapist at the HBOT center should collaborate.



HBOT should be considered for post-traumatic patients who have undergone trauma-focused psychotherapy with or without pharmacotherapy but continue to experience a significant symptom burden, **regardless of the time that had elapsed since the traumatogenic event.**

HBOT may be provided earlier in the treatment course for patients who exhibit severe symptoms and do not respond to, or cannot tolerate, psychotherapy or pharmacotherapy

HBOT is not recommended as a first-line therapy or for patients with minimal symptoms due to the lengthy nature of the treatment and its associated costs. Therefore, the patient's case manager (typically the treating psychiatrist for Israeli veterans) should assess the patient's condition and the available PTSD treatment options before referring the patient for an HBOT treatment course.

HBOT should not be initiated while exposure to traumatic events is still ongoing. Persistent exposure to trauma during the HBOT treatment course may undermine the therapy's potential effectiveness and compromise its outcome.

Continuation of psychotherapy during and after HBOT is required for the integration of therapeutic changes. That may include newly surfaced memories that may alter the patient's narrative, and new personal social and occupational insights that need to be sorted out and incorporated. Furthermore, stable psychotherapy will ensure ongoing support after the HBOT course is over. Intensification of therapeutic encounters are suggested when needed.

The psychotherapist should be informed that exposure therapy is not recommended during the HBOT treatment course. **Psychotherapy should be responsive and supportive, led by the thoughts and emotions that surface during treatment**, presumably by the biological effect of treatment.

Suicidal ideation is common among post-traumatic patients. Patients should be informed that symptom worsening may be accompanied by the emergence or intensification of suicidal thoughts, but these thoughts are likely to diminish as treatment progresses. If such thoughts arise at any time, day or night, patients should have a designated point of contact where they can seek support and guidance.

The issue of compensation, such as disability benefits or other support provided by governmental authorities for PTSD, significantly affects the course of symptoms and motivation for recovery. Therefore, the intensive and demanding course of HBOT should not be offered when the compensation claim is still unresolved.



Pre-Treatment Evaluation and Preparation

- The medication regimen should be adjusted and stabilized before treatment.
- Benzodiazepines should be withheld, if possible.
- Smoking should be ceased before beginning HBOT.
- Self-regulation techniques should be taught.

Smoking cessation

Concerns have been raised regarding the effect of HBOT on pulmonary function, as some studies suggest potential toxicity, such as reduced forced vital capacity and impaired diffusion(68). To minimize this risk, smokers were excluded from both clinical studies and routine practice, and baseline pulmonary function tests were conducted to rule out uncontrolled obstructive lung disease.

Indeed, a study evaluating the effect of HBOT on pulmonary function revealed that the treatment can be considered safe(69). To ensure safety, patients should be instructed to quit smoking before starting HBOT.

Smoking is highly prevalent among the post-traumatic population. Visiting the treatment center, learning about the potential effects of HBOT on post-traumatic symptoms, and engaging with the treating staff may enhance motivation for smoking cessation. Therefore, smokers should be encouraged to attend an initial meeting at the center. 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 strengths.

Adjustment of medication regimen

Benzodiazepines depress multiple gene expression in the brain (70, 71), including the neuroplasticity-related genes and should thus be withheld if possible before starting HBOT. In some cases, severe insomnia and or distress may accompany benzodiazepines cessation and thus recommendations should be based on heavy consideration of this cost.

Adjusting and stabilizing the dose of other psychiatric medications should be recommended before HBOT, as HBOT-related symptom fluctuations may complicate the assessment of medication effects and make it difficult to evaluate the impact of HBOT-both its desired effects and potential adverse reactions.

Cannabis use is very common among post-traumatic veterans, offering significant acute symptom relief. However, its long-term effects may include reduced motivation, memory impairment, and other cognitive challenges. The self-titrating nature of cannabis dosing makes it well-suited to the fluctuating symptom load during HBOT. It allows patients to manage



symptom exacerbations by increasing the dose when needed, while also enabling them to reduce or withhold cannabis use when symptoms subside. Cannabis should not be consumed by smoking but rather through vaporization or as a tincture.

Acquisition of self-regulation techniques

Prior to the initiation of HBOT, training in self-regulation techniques is recommended. These may include trauma-focused yoga, physical activity, and grounding techniques, tailored to each patient's needs. Acquiring these skills before treatment can help ensure optimal management of symptom exacerbation, should it occur during the treatment course.

Pre-Treatment Analyses

- Functional and structural brain imaging
- Evaluation of symptoms
- Pre-treatment meeting for the integration of clinical and imaging-based finding

- Brain MRI

Brain MRI should be performed at baseline to rule out alternative diagnoses.

- Functional brain imaging (SPECT or fMRI)

Functional brain imaging allows most patients to visualize, often for the first time, abnormalities in the function of their temporal and frontal lobes. Encountering an objective measure that highlights dysfunction in specific brain regions can be crucial for self-validation, for reducing feelings of shame, and for challenging the stigma associated with their condition. Additionally, it supports patient dedication by fostering understanding of their condition and enhances cooperation with the protocol of a treatment aims to target these changes. Functional brain imaging can also serve as a baseline for comparison with imaging conducted at the end of treatment to assess the effects of the intervention.

- CAPS-V inventory

An interview by a therapist with expertise in trauma for the evaluation of symptom load is done as part of the pretreatment evaluation. The inventory will contribute to patient's and staff



understanding of PTSD severity. Another essential role of this inventory is educating patients about the symptoms that are part of their post-traumatic stress disorder. This awareness can help patients recognize changes in their symptoms over time, enhancing their engagement in the treatment process.

A pre-treatment meeting for integration

Following the completion of the pre-treatment evaluation and before the beginning of HBOT, an integration meeting with a leading therapist is conducted. The purpose of the meeting is to review the patient's symptoms and brain imaging and integrate this information for a better understanding of the patient's baseline condition.

The therapist will re-inform the patient about potential adverse effects that may arise during treatment, including the potential surfacing of inaccessible memories and temporary worsening of symptoms. They will also outline the resources available within and outside the center to support the patient if needed.

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

Treatment Corse

- HBOT sessions should be scheduled at the same time each day to promote the establishment of a routine.
- Psychotherapy should be provided by a therapist familiar with the effects of HBOT and how to manage them
- Physical activity, nutritional consultation, and yoga practice will have positive effects on patients' adherence and on treatment results.

HBOT

The HBOT protocol consists of 60 daily sessions, with the pressure of 2ATA and 90min 100% O₂ with 5 minutes air brakes every 20 minutes.

The treatment should be provided at the same time each day to enable the patient to create routine, and preferably with the same fallow patients within the multiplace chamber. The treatment should be provided in a multiplace facility, with a trained nurse present in the chamber and available if any assistance is needed.

Psychotherapy

Weekly meetings with the center's therapist should be scheduled to monitor symptoms, strengthen self-regulation techniques, and assess any worsening symptoms or surfacing



memories. Psychoeducation is an essential treatment tool, providing a biological rationale for the symptoms that arise.

In the case of surfacing memories, patients will be encouraged to describe the event and answer questions about the place, time, and sequence of events to support verbal representation of the new memory. Daily meetings may be necessary if the memory evolves gradually or if special support is needed. Self-regulation techniques and psychoeducation are essential elements during these events.

In some cases, an unfamiliar memory of childhood or sexual abuse may surface, necessitating consultation with an expert in these fields.

Occupational and social rehabilitation should be discussed with the therapist toward the end of the treatment course.

Additional support

Techniques that contribute to better self regulation should be encouraged. Trauma-sensitive yoga focuses on regulating and balancing the autonomic nervous system through the tools of yoga: movement, breathing, concentration, and relaxation. The guiding principles of this approach include restoring and establishing a sense of safety, fostering personal efficacy and agency, and enhancing vagal activity (72, 73).

Physical activity should be promoted both for its role in self-regulation and its positive effect on neurogenesis. Nutritional consultation is essential to ensure adequate levels of elements such as B12 and iron, as well as sufficient protein intake to support recovery. At the same time, a low-carbohydrate diet should be recommended to avoid fluctuations in glucose levels, which can negatively affect mood and stress.

Psychiatric consultation

Changes in psychiatric regimens are not recommended during the treatment course, as they may complicate the identification of HBOT's effects on mood and stress. In cases of worsening distress, short-term or 'as-needed' treatments, such as quetiapine or olanzapine, may be provided. Benzodiazepines should be avoided.



Post-Treatment Evaluation and Treatment Summary

- Patient narrative
- Symptoms load
- Changes in brain activity and structure
- Integration
- The full treatment effect may evolve in a course of few months

Post-Treatment Analysis

- Functional brain imaging (fMRI and/or SPECT)

The end of treatment analysis will enable comparison to pre-treatment functional imaging. Areas with significant changes will be marked.

- CAPS-V inventory

An interview by a therapist with expertise in trauma for the evaluation of symptom load after treatment will provide data about the symptom's status and evaluation of changes in symptoms severity following treatment.

End of treatment meeting

The meeting typically takes place 4 to 6 weeks after the completion of the HBOT course, following the administration and analysis of end-of-study tests. It begins with the patient's subjective assessment of the treatment effect, focusing on the anticipated versus actual outcomes. Special attention should be given to the potential surfacing of unfamiliar memories. The therapist must ensure that any such memories received adequate attention and processing. The meeting then proceeds to evaluate changes in symptom load as reported in questionnaires, alongside changes in brain perfusion and structure. Emphasis should be placed on integrating the observed changes in symptoms with alterations in brain activity.

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



Indications for additional HBOT sessions

Additional HBOT sessions should not be initiated immediately after completing the initial treatment course (which may extend to 70 sessions, based on the physician's judgment). This is because neuroplasticity-driven improvements often continue for up to three months post-treatment, reflecting the sustained biological processes activated during HBOT. Allowing this natural progression is essential to maximize therapeutic benefits before considering further sessions.

A repeated course of 40 to 60 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 both the patient's therapist and a hyperbaric physician with expertise in treating PTSD, ensuring that additional treatment aligns with the patient's ongoing clinical needs.

Post treatment follow-ups

Following the treatment course, as core symptoms improve, it is important to address longstanding avoidance behaviors. These habits should be gradually challenged, supported by structured plans for occupational and social rehabilitation. Notably, **even patients who were unsuccessful in achieving rehabilitation before undergoing HBOT may find new opportunities for integration and recovery as their symptoms improve.**



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