
Evidence Brief: Hyperbaric Oxygen Therapy for Traumatic Brain Injury and/or Post-traumatic Stress Disorder

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the [program website](#).

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

Key Findings

- **Acute moderate to severe TBI:** For patients hospitalized with acute moderate to severe TBI, available evidence suggests HBOT can reduce mortality and coma severity more than standard care, but it is unclear whether HBOT improves longer-term functionality. In patients with acute TBI, severe pulmonary complications and seizures may occur. Because HBOT protocols varied widely across available trials, clarity is needed on the optimal HBOT protocol for moderate to severe TBI.
- **Chronic mild TBI (mTBI):** When pooled, evidence on HBOT for chronic mTBI shows that HBOT does not lead to short-term improvements in post-concussion and PTSD symptoms compared to sham, and sparse longer-term evidence suggests symptom improvement after HBOT is not durable. HBOT appears to be well-tolerated by patients with chronic mTBI, with the most common side effect being mild barotrauma.
- A targeted review of outcome measures for TBI and/or PTSD found that similar measures are used in HBOT trials and studies of other treatments for TBI and/or PTSD, and across VA and non-VA HBOT trials.
- Decisions about whether additional research is warranted must consider whether patient, provider, and system resources required for HBOT would be better directed toward other approaches. One future research direction could be to examine whether features of the HBOT treatment experience (*eg*, coordinated engagement with providers and other patients) are themselves active intervention components that could be incorporated into more widely implementable treatments for chronic post-concussion symptoms.

Traumatic brain injury (TBI) and PTSD can often result in similar prolonged symptoms. Many people with chronic mTBI and/or PTSD do not achieve symptom remission with currently recommended treatments, and HBOT has been explored as a treatment alternative for those with persistent symptoms. HBOT is used to increase the supply of oxygen to blood and tissues by delivering 100% medical-grade oxygen inside a chamber where the air pressure is raised to at least 1.4 times greater than normal. Evidence from case series suggesting that HBOT may lead to improved cerebral blood flow, PTSD and post-concussion symptoms, and patient quality of life has not been well-replicated in randomized clinical trials. HBOT has not been FDA-cleared for treatment of TBI and/or PTSD, and the efficacy of HBOT in this application continues to be debated.

Background

The Evidence Synthesis Program Coordinating Center is responding to a request from the VA Health Services Research and Development Service for an updated evidence brief on the use of hyperbaric oxygen therapy for the treatment of traumatic brain injury and/or post-traumatic stress disorder, in response to the Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019 (“Hannon Act”). Findings from this updated evidence brief will be used to inform a report submitted to the Committees on Veterans Affairs of the US Senate and the US House of Representatives in response to Section 702 of the Hannon Act.

Methods

To identify studies, we searched MEDLINE®, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and other sources up to October 2020. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See our PROSPERO protocol for full study details.

The present review updates a 2018 review by the VA Evidence Synthesis Program (ESP) and includes 2 randomized controlled trials completed since the earlier review. Findings of this updated synthesis align with those of the previous ESP review. The updated findings include:

Acute TBI. For patients hospitalized with acute moderate to severe TBI, available evidence suggests HBOT can reduce mortality and coma severity more than standard neurosurgical care, but it is unclear whether HBOT improves longer-term functionality. Patients with acute severe TBI who receive HBOT may experience significant adverse effects, including severe pulmonary complications and seizures. Most HBOT trials in patients with acute TBI did not include current Service members or Veterans with blast-related TBI or patients with moderate TBI; therefore, evidence may be most applicable to patients with severe TBI from other causes.

Treating patients with acute moderate to severe TBI represents a considerably different clinical scenario than treatment of chronic mTBI (the most common form of TBI in Veterans) and prioritizes life-saving interventions typically delivered to hospitalized patients within hours or days of injury. In this application, evidence suggests HBOT may offer near-term benefits. However, because HBOT protocols varied widely across available trials and severe adverse effects may occur, clarity is needed on the protocol that optimally balances benefits and risks of HBOT for patients with acute moderate to severe TBI.

Chronic mTBI. When pooled, evidence on HBOT for chronic mTBI shows that HBOT does not lead to short-term improvements in post-concussion and PTSD symptoms compared to sham. Sparse longer-term evidence suggests symptom improvement after HBOT is not durable. HBOT appears to be well-tolerated by patients with chronic mTBI, with the most common side effect being mild barotrauma.

In several included sham-controlled trials, short-term symptom improvement was similar in both HBOT and sham groups, which suggests observed symptom change is likely the result of participation and/or placebo effects that occur because of the intensity of the HBOT intervention and its sham equivalent. Participation and placebo effects can result from the experience of accessing and receiving care (including sham treatment); engaging with and being engaged by providers, nurses, and other caring staff (for screening, intervention or sham delivery, and outcome assessment); and from patient and provider expectancies of treatment response.

PTSD without TBI. Available evidence is not applicable to PTSD-diagnosed patients *without* a co-occurring TBI because no trials included these patients.

Typically, health systems assign a low priority to treatments such as HBOT that have so far failed to show conclusive benefit over placebo, sham intervention, or usual care, and consider manufacturers and advocates to have the burden to prove that the intervention can work. In the VA context, decisions about whether additional research is warranted must consider whether patient, provider, and system resources required for HBOT would be better directed toward other approaches. It is also important to recognize that a lack of effect when an intervention is compared to an inactive condition does not necessarily mean the intervention has no benefits. As noted in our original review, evidence on HBOT (and evidence on other treatments that has similar characteristics, such as acupuncture for chronic pain) suggests that the *features* of the HBOT therapeutic experience may act together to create conditions that lead to improved patient symptoms, at least in the short term. One future research direction could be to examine whether

features of the HBOT treatment experience (*eg*, coordinated engagement with providers and other patients) are themselves active intervention components that could be incorporated into more widely implementable treatments for chronic post-concussion symptoms.

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The Evidence Synthesis Program (ESP) Coordinating Center is responding to a request from the VA Health Services Research and Development Service for an update to the 2018 ESP evidence brief¹ on the use of hyperbaric oxygen therapy (HBOT) to treat Veterans and non-Veterans with traumatic brain injury (TBI) and/or post-traumatic stress disorder (PTSD), in response to the Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019 (“Hannon Act”). A secondary aim of this update was to provide an overview of assessment tools for measuring TBI and PTSD symptoms. Findings from this evidence brief will be used to inform a report to the Committees on Veterans Affairs of the US Senate and the US House of Representatives in response to Section 702 of the Hannon Act.

BACKGROUND

Hyperbaric Oxygen Therapy

HBOT is designed to increase the partial pressure of oxygen in the blood and tissues through inhalation of pure oxygen in an environment pressurized to at least 1.4 times normal atmospheric absolute (ATA) pressure at sea level (most regimens use 2.0-2.8 ATA).² The increase in arterial oxygen partial pressure has widespread effects, including reversal of hypoxia in injured tissues, changes in connective and immune cell function, inhibition of inflammation, reduction in swelling, and release of stem cells.³⁻⁵ Delivery of HBOT involves use of medical-grade oxygen, and HBOT chambers are ideally operated by specially trained hyperbaric technicians under the supervision of a clinician.⁶

HBOT is an established treatment for decompression sickness, which can occur in scuba divers who have resurfaced from pressurized environments, and has been used for other indications such as treatment of infections or wounds.⁷ Fourteen indications are currently cleared for HBOT device use by the FDA and maintained by the Undersea & Hyperbaric Medical Society (UHMS), including treatment of air or gas embolism, carbon monoxide poisoning, decompression sickness, and soft tissue necrosis (see Appendix A in supplemental materials for full list).⁸ HBOT protocols vary based on the indication, its severity, and patient treatment tolerance and response. HBOT sessions can last 60 to 90 minutes and be delivered 1 or more times each day up to 5 days per week, for as little as 10 days or as long as 6 to 10 weeks. Over the course of treatment, patients frequently interact with hyperbaric technicians, nurses, and other patients.

Treatment of Prolonged Symptoms of TBI and/or PTSD

Chronic mild TBI (mTBI) and PTSD often result in similar prolonged symptoms. Patients with chronic mTBI experience physical (*eg*, headache, dizziness, vision), cognitive (*eg*, memory, focus, judgment), and emotional (*eg*, depression, anger, anxiety) symptoms that last longer than 3 months following their injury and may take 6 months to a year to completely resolve.⁹⁻¹¹ PTSD can also result in cognitive and mood problems, sleep issues, and difficulties with concentration, as well as unique symptoms such as hypervigilance, flashbacks, or re-experiencing of a traumatic event.¹² Moderate to severe TBI may result in similar cognitive impairments and behavioral

changes, although patients can also experience disability, elevated risk of neurological diseases that can cause functional impairment, and increased risk of death.^{13,14} Nineteen to 36% of patients with moderate to severe TBI do not survive.¹⁵

Despite limited available evidence on efficacious treatments for mTBI,^{16,17} VA/DoD guidelines recommend a coordinated stepped-care treatment approach using psychoeducation, cognitive rehabilitation, nonpharmacologic interventions (eg, sleep hygiene, education, dietary modification, physical therapy, and relaxation), behavioral health treatments, and/or pharmacologic interventions.¹⁸ VA/DoD guidelines for PTSD recommend trauma-focused psychotherapy as primary treatment over pharmacologic and other non-pharmacologic interventions.¹⁹ (See Appendix B in supplemental materials for full list of relevant guidelines.) Treatment of acute moderate to severe TBI represents a different clinical scenario from treatment of chronic mTBI, and prioritizes life-saving measures such as decompressive craniectomy, barbiturate administration, and seizure prophylaxis.²⁰

Use of HBOT for TBI and/or PTSD

Some patients with chronic mTBI and/or PTSD do not experience symptom improvement with recommended therapies,⁹⁻¹¹ and HBOT has been explored as a treatment alternative.^{21,22} Evidence to support HBOT in this application has been drawn from both animal and human studies. In animal models of acute TBI, HBOT improves intermediate disease markers such as tissue oxygenation, neuronal stem cell proliferation, and inflammation,²³ while in patients hospitalized with acute TBI, HBOT has been shown to reduce markers of central nervous system inflammation.²⁴ In case series of patients with mTBI, substantial improvements in cerebral blood flow, post-concussion symptoms, and quality of life have been reported after HBOT.^{4,25} Importantly, these large improvements have not been well-replicated in randomized clinical trials,¹ suggesting that results of case series may not accurately characterize HBOT efficacy.

Clinical trials are intended to provide a rigorous assessment of whether HBOT causes improvement in TBI and/or PTSD symptoms, but trial findings have been challenging to interpret and widely debated. An ongoing area of controversy is whether HBOT leads to genuine treatment effects or, given the intensity of the intervention, instead produces participation (or Hawthorne) effects and/or placebo effects.²⁶⁻²⁸ These can occur when patients or providers know who has been selected to receive treatment (*ie*, unblinded), or when patients perceive they are receiving treatment because of sensory stimuli (eg, pressure changes or sounds associated with treatment) or the intensive engagement of providers, nurses, and other staff that accompanies treatment delivery. Activities associated with accessing a trial, such as consenting and completing baseline assessments, may also induce participation effects. Participation effects can impact both treatment and control groups in clinical trials and may lead to inconsistent, misleading, or difficult to interpret trial findings.^{26,27,29}

Evidence available at the time of the previous ESP review¹ was inconclusive about the efficacy of HBOT for mTBI and PTSD, and use of HBOT to treat TBI or PTSD has not been FDA-cleared or endorsed by clinical practice guidelines or payer policies. Consequently, use of HBOT for this purpose has remained limited. Research has continued, however, and since the release of the previous ESP review, additional trials have been completed. The purpose of the current review was to determine whether findings of these trials, when synthesized with earlier evidence, provide clarity on HBOT efficacy for TBI and/or PTSD.

METHODS

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO/>; registration number CRD42020216736).

KEY QUESTIONS

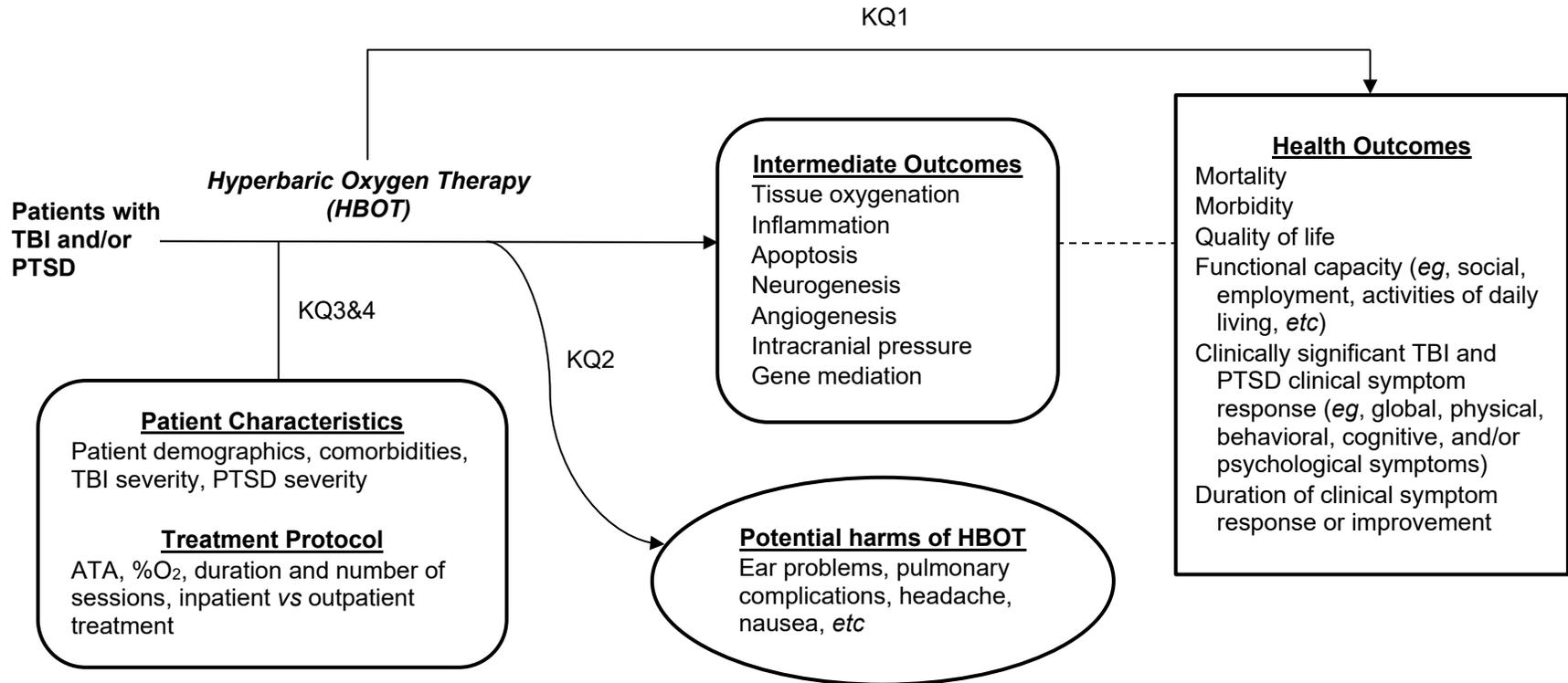
The following key questions (KQs) were the focus of this review:

- KQ1:* What are the potential benefits of HBOT for the treatment of TBI and/or PTSD?
- KQ2:* What are the potential risks of using HBOT for the treatment of TBI and/or PTSD?
- KQ3:* Do the benefits or risks of HBOT differ per patient characteristics (*eg*, patient demographics, comorbidities, disease severity)?
- KQ4:* Do the benefits or risks of HBOT differ per treatment protocol (*eg*, number of sessions, amount of pressure, inpatient vs outpatient treatment)?

ANALYTIC FRAMEWORK

The analytic framework shown in Figure 1 provides a conceptual overview of this review. The population of interest was patients with TBI and/or PTSD. Eligible outcomes included health and other clinically significant outcomes (Key Question 1) and treatment harms (Key Question 2). We did not consider intermediate outcomes associated with HBOT (*eg*, tissue oxygenation), as the purported treatment mechanism of HBOT implies that changes in intermediate outcomes results in changes in eligible patient-relevant outcomes. Whether benefits and/or risks of HBOT differ by patient characteristics (*eg*, patient demographics, comorbidities, disease severity) or treatment protocol (*eg*, number of sessions, amount of pressure, inpatient vs outpatient treatment) was also of interest (Key Questions 3 and 4).

Figure 1. Analytic Framework



Abbreviations. ATA=atmospheres absolute, KQ=key question, PTSD=post-traumatic stress disorder, TBI=traumatic brain injury, %O₂=percent oxygen.

ELIGIBILITY CRITERIA

The ESP included studies that met the following criteria:

- **Population:** Patients with TBI, PTSD, or the co-occurrence of TBI and PTSD
- **Intervention:** HBOT, any protocol (per Undersea & Hyperbaric Medical Society)
- **Comparator:** Any (eg, sham HBOT, no treatment, standard care)
- **Outcomes:**
 - **Benefits:** Mortality, morbidity, quality of life, functional capacity (eg, social, employment, activities of daily living, etc), TBI and/or PTSD symptom improvement (eg, mean change in symptom response), clinically significant TBI and PTSD clinical symptom response (as defined in included studies [eg, proportion of patients meeting a preset threshold for symptom improvement]), and duration of clinical symptom response or improvement. We accepted any definition of clinically significant clinical symptom response. We excluded intermediate physiologic measures, such as intracranial pressure, cerebrospinal fluid lactate levels, or changes in cerebral blood flow.
 - **Harms:** Any (ear problems, pulmonary complications, headache, nausea, etc)
- **Timing:** Any
- **Setting:** Any
- **Study design:** Systematic reviews, randomized controlled trials, and concurrently controlled cohort studies. We considered case series (ie, $N > 1$) only to address gaps in evidence from studies with control groups. We excluded case reports (ie, $N = 1$).

DATA SOURCES AND SEARCHES

To identify articles relevant to the key questions, a research librarian searched Ovid MEDLINE, Ovid PsycINFO, Ovid CENTRAL, ClinicalTrials.gov, and PTSDpubs, as well as AHRQ, Cochrane Database of Systematic Reviews, and HSR&D through October 2020 using terms for *hyperbaric oxygen therapy*, *traumatic brain injury*, and *post-traumatic stress disorder* (see Appendix C in the supplemental materials for complete search strategies). Additional citations were identified from hand-searching reference lists and consultation with content experts. We limited the search to published and indexed articles involving human subjects available in the English language. Study selection was based on the eligibility criteria described above. Titles, abstracts, and full-text articles were reviewed by 1 investigator and checked by another. All disagreements were resolved by consensus or discussion with a third reviewer.

As noted, an objective of the review update was to provide an overview of assessment tools for measuring PTSD and TBI symptoms. We conducted a secondary non-systematic search to identify guidelines and systematic reviews for TBI and PTSD assessment tools through the Cochrane Database of Systematic Reviews and the ECRI Guidelines Trust database. Because we limited our search to these sources, we did not carry out additional quality or strength of evidence assessments on these reports.

DATA ABSTRACTION AND ASSESSMENT

Effect information and population, intervention, and comparator characteristics were abstracted from all included studies, and study authors were queried for missing effect information when necessary. The internal validity (risk of bias) of each included study was rated using the

Cochrane's Risk of Bias 2.0 Tool.³⁰ All data abstraction and internal validity ratings were first completed by 1 reviewer and then checked by another; disagreements were resolved by consensus or discussion with a third reviewer.

We graded the strength of the evidence for each outcome based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.³¹ This approach provides a rating of confidence in reported findings based on trial methodology (design, quality, and risk of bias), consistency (whether effects are in the same direction and have a consistent magnitude), and directness (whether assessed outcomes are clinically important to patients and providers). When information on precision of findings (eg, confidence intervals) is available, certainty of evidence is also evaluated. For this review, we applied the following general algorithm: *high strength* evidence consisted of multiple, large trials with low risk of bias and consistent and precise findings; *moderate strength* evidence consisted of multiple trials with low to unclear risk of bias and consistent and precise findings; *low strength* evidence consisted of a single trial, or multiple small trials, with unclear to high risk of bias and/or inconsistent or imprecise findings; and *insufficient* evidence consisted of a single trial with unclear or high risk of bias, or no available trials. Directness of findings was addressed by requiring included studies to report clinically relevant outcomes.

SYNTHESIS

Trial findings were organized by condition (mTBI or moderate-severe TBI), comparator (sham or no treatment/standard care), and outcome type (post-concussion or PTSD symptoms). When treatment and comparator protocols were sufficiently similar and 2 or more effect estimates from similar timepoints were available, we quantitatively synthesized (meta-analyzed) available effect information to improve statistical power and overcome potential analytic limitations of included trials (eg, significance levels not adjusted for multiple comparisons). When effect data could not be pooled, evidence was synthesized narratively.

Effect sizes for meta-analyses were mean differences between treatment and comparison groups following the treatment course or control period. Standard deviations of means, when not readily available, were calculated from 95% confidence intervals or independent or dependent *t*-tests (calculations using dependent *t*-tests assumed a correlation of 0.8 between baseline and post-treatment means). When the same outcome scale was used across trials, raw mean difference (MD) effect sizes were used; when different measures of the same outcome were available, bias-adjusted standardized mean differences (Hedges' *g*) were employed.

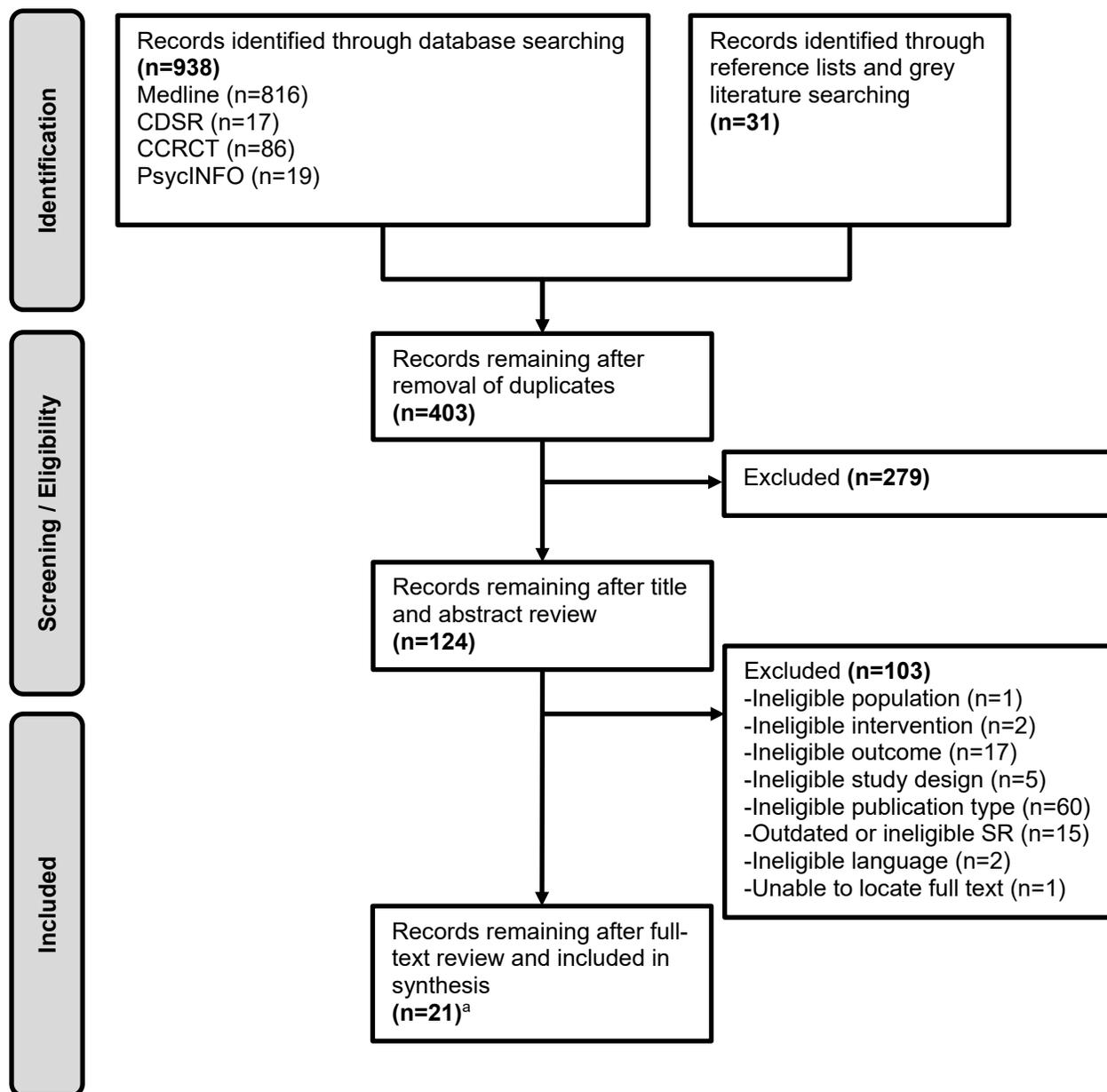
Random-effects models were used for all meta-analyses. For independent effect data, exact confidence intervals for small meta-analyses were calculated using the method developed by Michael et al.³² When trials reported multiple effect estimates, multivariate random-effects meta-analyses were used to account for dependency among effect estimates, and cluster-robust confidence intervals were calculated for overall effect estimates. Within-trial correlation among dependent effects was assumed to be 0.8; sensitivity analyses using a correlation of 0.3 were conducted to ensure findings were not impacted by this assumption. Heterogeneity in effects was calculated using the restricted maximum-likelihood estimator and evaluated using 95% prediction intervals.^{33,34} Meta-analyses were conducted using the *metafor*³⁵ package for R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 2) summarizes the results of the study selection process (full list of excluded studies available in Appendix D in supplemental materials).

Figure 2. Literature Flowchart



Notes. ^a14 studies in 21 publications. This reflects fewer publications than the original ESP evidence brief due to exclusion of systematic reviews and focus on primary studies with outcomes of interest.

Abbreviations. CCRCT=Cochrane Central Register of Controlled Trials, CDSR=Cochrane Database of Systematic Reviews, SR=systematic review.

LITERATURE OVERVIEW

Our search identified 403 potentially relevant articles. We included 14 trials (in 21 publications),^{3,24,36-54} which are summarized in Table 1 (see Appendix E in supplemental materials for full trial details). Six trials included patients with chronic mTBI,^{3,38,40,43,51,54} 7 trials included patients with acute moderate to severe TBI,^{24,36,42,44-47} and 1 trial did not specify TBI severity.⁴⁸ Trials in patients with chronic mTBI included patients with or without PTSD, but no trials included patients with PTSD alone (*ie*, without a co-occurring TBI). The median sample size of included trials was 60 participants (range: 30-320). We identified 2 underway trials (see Appendix F in supplemental materials) examining HBOT use in patients with TBI.

Mild TBI

Trials examining HBOT for mTBI used 30 to 40 sessions of HBOT and compared the treatment group to either a sham condition or to a no treatment or standard care condition. In a sham-controlled trial, patients randomized to the control group experience an intervention that mimics the active treatment condition but is designed to have no treatment effect; as a result, all patients remain blinded to whether they actually received treatment. Sham conditions in HBOT trials used a hyperbaric chamber filled with normal air (*ie*, less than 100% oxygen) at a lower pressure (1.2 to 1.3 ATA)^{43,51} or low oxygen (10.5%) delivered at 2.0 ATA³⁹ to simulate hyperbaric effects such as ear pressure and heating and cooling effects of pressurization. All included sham-controlled trials enrolled military members with at least 1 mTBI and persistent post-concussion symptoms lasting at least 3 months since their most recent TBI. Four trials^{38,40,43,51} assessed the proportion of participants with PTSD symptoms, which ranged from 36% to 65%. Trials using no treatment or standard care control conditions were not limited to military members, and participants in these trials were required to have 1 or more mTBIs with persistent post-concussion symptoms. Sham-controlled trials were generally at low risk of biases from randomization procedures, blinding of participants and outcome assessors, missing outcome data (attrition), and deviations from group assignments and trial protocols, while trials using a no treatment comparator were rated as unclear or high risk of bias primarily due to incomplete blinding and attrition. All trials in patients with mTBI were small (50-72 participants), likely limiting statistical power.

We identified 2 trials among patients with mTBI completed since the previous ESP review.¹ The first, known as BIMA, was a double-blind sham-controlled trial⁵¹ of 71 military Service members with at least 1 mTBI and post-concussion symptoms lasting at least 3 months. According to its registered protocol,⁵⁵ BIMA was a Phase II trial and the primary outcome was adverse events associated with treatment exposure. BIMA was not intended to determine efficacy of HBOT, instead aiming to identify outcomes (endpoints) for future efficacy trials from an extensive battery of outcome measures.^{51,55} Consequently, efficacy-related findings were considered exploratory and were derived from numerous statistical tests that were not adjusted to limit the possibility of false positives. In addition, participants receiving HBOT appeared to have more severe traumatic brain injuries, on average, than those assigned to the sham group, and the trial also suffered considerable attrition during extended outcome assessment (only 25% of participants originally allocated to HBOT completed the final long-term assessment).

The second new trial identified was a partially-blinded, Phase III, no treatment-controlled crossover trial⁴⁰ of 60 civilian and military participants with mTBI and post-concussion symptoms persisting for at least 6 months. In this trial, 65% of participants allocated to HBOT

completed the final assessment. Participants who dropped out had worse baseline PTSD and post-concussion symptoms than participants in HBOT or control groups. The difference in baseline post-concussion symptoms between drop-outs and control participants was significant, and the authors did not appear to report a statistical test for the difference in baseline post-concussion symptoms between drop-outs and HBOT participants; an overall test of the difference in baseline PTSD symptoms between HBOT, control, and drop-out groups was nonsignificant.

Moderate to Severe TBI

All trials investigating HBOT for moderate to severe TBI were included in the previous ESP review on HBOT efficacy for TBI with/without PTSD.¹ Most trials compared HBOT to standard neurosurgical care; 1 used a medication therapy control condition. In these trials, HBOT was used for acute treatment in hospitalized patients, often just hours or days after injury. HBOT treatment courses varied considerably among these trials. Those using HBOT at 1.5 ATA⁴⁵⁻⁴⁷ delivered the therapy in 1-hour sessions spaced 4 to 24 hours apart for as few as 3 days and as long as 2 weeks. Three of the 4 trials using higher-pressure HBOT^{24,36,42} (2.0-2.5 ATA) delivered HBOT once daily in longer sessions (70-120 minutes) for 10 to 20 sessions. One trial³⁶ repeated the course until the patient recovered or died. A final higher-pressure trial⁴⁴ administered 10 briefer sessions over 4 days. The majority of moderate to severe TBI trials included patients with severe TBI only; 1 trial⁴² included hospitalized patients with moderate or severe TBI. Findings of these trials were at unclear or high risk of bias due to lack of blinding of participants and/or outcome assessors, unclear or high levels of deviations from HBOT protocols in several trials, and exclusion of patients with complications from the analysis in 1 trial.⁴² Although 2 trials were comparatively large (168-320 participants), the majority of trials were small (30-60 participants).

Outcome Measurement

Across trials, measurement of symptoms varied by TBI severity because of differences in the physiology of injury and main outcomes of interest. In trials among patients with mTBI, symptoms of TBI and PTSD were typically assessed using the Rivermead Post-concussion Symptom Questionnaire-13 (RPQ-13; 3 trials), the Neurobehavioral Symptom Inventory (NSI; 3 trials), and the PTSD Checklist (PCL; 5 trials). One trial⁵³ in mTBI patients used the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) tool, which the VA/DoD guideline on concussion and mild TBI recommends against using for routine diagnosis and care of patients with symptoms attributed to mTBI.¹⁸ Another mTBI trial⁵⁰ developed a composite outcome scale based on several existing tools to assess cognitive, physical, and emotional symptoms. Trials in patients with acute moderate to severe TBI used the Glasgow Coma and Outcome Scales (GCS/GOS; 6 trials) and measured patient mortality (4 trials).

Measurement of symptoms was comparable in trials of military/Veteran and civilian populations. Both groups of trials used similar tools and timing of assessments, and generally assessed symptom improvement using mean outcome scores rather than cut-off values. All trials in patients with mTBI assessed HBOT efficacy post-treatment (*ie*, immediately following 8- to 12-week treatment course); 2 of 4 sham-controlled trials and 1 of 2 standard care or no treatment-controlled trials conducted longer-term follow-up assessments, although follow-up timing varied considerably across trials. In trials of patients with moderate to severe TBI, timing of outcome assessments ranged from immediately following to 6 months after treatment, or was not reported.

Outcome Measurement in HBOT vs non-HBOT Studies

Measurement of treatment efficacy in trials of HBOT for TBI with/without PTSD uses similar tools to those used for other therapies. Using a targeted search of systematic reviews on treatments (other than HBOT) for TBI and PTSD, we identified 24 tools or measures for TBI symptoms and 30 tools or measures for PTSD symptoms (Appendix G in supplemental materials). A 2018 report on treatment of PTSD by the Agency for Healthcare Research and Quality includes a comprehensive list of PTSD outcome assessment tools.⁵⁶ Measurement tools and scales used in HBOT trials and studies of other treatments included the PTSD Checklist, the Rivermead Post-concussion Symptom Questionnaire, and the Glasgow Coma and Outcomes Scales. The most commonly reported tool not used in HBOT trials was the Clinician Administered PTSD Scale.

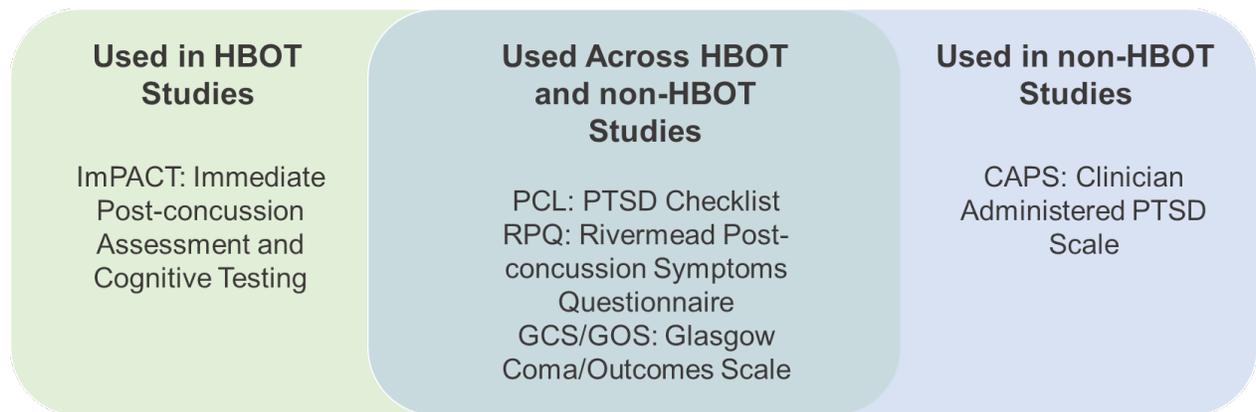


Table 1. Characteristics of Included Trials

Trial	Sample Size Follow-up	Population	HBOT Characteristics	Control	Outcomes Assessed
<i>Mild TBI</i>					
BIMA Weaver, 2018 ^{37,41,50,51}	N=71 PT, 6 mo, 12 mo ^a	Military personnel with persistent post-concussion symptoms 3-5 yrs after mTBI	1.5 ATA 40 1-hour sessions (> 99% oxygen) over 12 wks	Sham HBOT: 1.2 ATA (room air)	PTSD and post-concussion symptoms (PCL, RPQ, NSI, <i>etc</i>), quality of life (WHOQOL)
Cifu, 2014 ^{38,39,49}	N=61 PT, 5.5 mo	Military personnel with persistent post-concussion symptoms ≥ 3 mo after mTBI	2.0 ATA 40 1-hour sessions (75% oxygen [1.5 ATA equivalent] or 100% oxygen) over 10 wks	Sham HBOT: 2.0 ATA, 10.5% oxygen (1.0 ATA equivalent)	PTSD and post-concussion symptoms (RPQ, PCL, <i>etc</i>)
HOPPS Miller, 2015 ^{37,43,50}	N=72 PT, 3 mo	Military personnel with persistent post-concussion symptoms ≥ 4 mo after mTBI	1.5 ATA 40 1-hour sessions (100% oxygen) over 10 wks	Sham HBOT: 1.2 ATA or standard post-concussion care only	PTSD and post-concussion symptoms (RPQ, NSI, PCL, <i>etc</i>), quality of life (SF-36)
Wolf, 2012 ⁵²⁻⁵⁴	N=50 PT	Military personnel with persistent post-concussion symptoms after mTBI	2.4 ATA 30 90-min sessions (100% oxygen) over 8 wks	Sham HBOT: 1.3 ATA	PTSD and post-concussion symptoms (ImPACT, PCL, <i>etc</i>)
Boussi-Gross, 2013 ³	N=56 PT	Patients with persistent post- concussion symptoms 1-6 yrs after mTBI	1.5 ATA 40 1-hour sessions (100% oxygen), 5 days/wk	No treatment	Cognitive function, quality of life (EQ-5D)
Harch, 2020 ⁴⁰	N=63 PT, 4 mo	Patients with persistent post- concussion symptoms ≥ 6 mo after mTBI	150 kPa (approx. 1.5 ATA) 40 1-hour sessions, 5 days/wk	No treatment	PTSD and post-concussion symptoms (NSI, PCL, <i>etc</i>), quality of life (QoL after brain injury)
<i>Moderate to Severe TBI</i>					
Artru, 1976 ³⁶	N=60 PT, 12 mo	Comatose, hospitalized patients with severe head injuries	2.5 ATA 10 daily 1.5-hour sessions, 4 days no session, repeated until patient recovered consciousness or died	Standard care (details NR)	Mortality, persistent coma, consciousness recovery
Lin, 2008 ⁴²	N=44 PT, 4 mo, 7 mo	Hospitalized patients with moderate to severe TBI	2.0 ATA 20 2-hour sessions (100% oxygen), once a day for 20 days over 4 wks	Standard care (details NR)	Glasgow Coma Scale and Glasgow Outcome Scale

Rockswold, 1985 ⁴⁵	N=30 3.5 mo	Comatose, hospitalized patients with severe brain injury	1.5 ATA 1-hour sessions (100% oxygen) every 4-8 hours for 2 wks until patient was brain dead or awake	Standard intensive neurosurgical treatment	Mortality and Glasgow Outcome Scale
Rockswold, 1992 ⁴⁶	N=168 12 mo	Comatose, hospitalized patients with severe brain injury	1.5 ATA 1-hour sessions (100% oxygen) every 8 hours for 2 wks until patient was brain dead or awake	Standard intensive neurosurgical treatment	Mortality and Glasgow Outcome Scale
Rockswold, 2013 ⁴⁷	N=42 6 mo	Hospitalized patients with severe brain injury	1.5 ATA 1-hour sessions (100% oxygen) followed by 1.0 ATA every 24 hours for 3 days	Standard intensive neurosurgical treatment	Mortality and Glasgow Outcome Scale
Xie, 2007 ²⁴	N=60 PT, NR	Hospitalized patients with severe brain injury	0.2 - 0.25 mPa (approx. 2.0 - 2.5 ATA) 10 70-80 min sessions, once a day for 10 days	Standard neurosurgical therapy	Glasgow Coma Scale
Ren, 2001 ⁴⁴	N=55 PT, 6 mo	Hospitalized patients with severe brain injury	0.25 mPa (approx. 2.5 ATA) 30-40 40-60-minute sessions (100% oxygen), delivered in 10 session increments over 4 days	Dehydrating, cortical steroid, and antibiotic therapy	Glasgow Coma Scale and Glasgow Outcome Scale
Unclear TBI Severity					
Shi, 2003 ⁴⁸	N=320 PT, 6 to 18 mo	Patients with post injury symptoms \geq 3 mo after TBI ^b	0.1 mPa (approx. 1.5 ATA) 10 90-min sessions (96% oxygen) over 10 days	Medication therapy (details NR)	Symptom improvement ^c

Notes. Follow-up time points are inclusive of treatment period (*ie*, from baseline). ^a24-36 month extended follow-up with substantial attrition; ^bTBI severity not specified; ^cno details provided on specific measurement tools.

Abbreviations. ATA=atmospheres absolute, BIMA=Brain Injury and Mechanisms of Action of HBO2 for Persistent Post-concussive Symptoms after Mild TBI study, EQ-5D=EuroQoL-5 Dimension, HBOT=hyperbaric oxygen therapy, HOPPS=Hyperbaric Oxygen Therapy for Persistent Postconcussive Symptoms after Mild Traumatic Brain Injury study, ImPACT=Immediate Post-concussive Assessment, kPa=kilopascal pressure unit, mo=month, MPa=megapascal pressure unit, mTBI=mild TBI, NR=not reported, NSI=Neurobehavioral Symptom Inventory, PCL=PTSD Checklist, PT=immediately post-treatment, RPQ=Rivermead Post-concussion Symptom Questionnaire, TBI=traumatic brain injury, WHOQOL=World Health Organization Quality of Life Assessment, wks=weeks.

EFFICACY OF HBOT FOR TBI WITH/WITHOUT PTSD

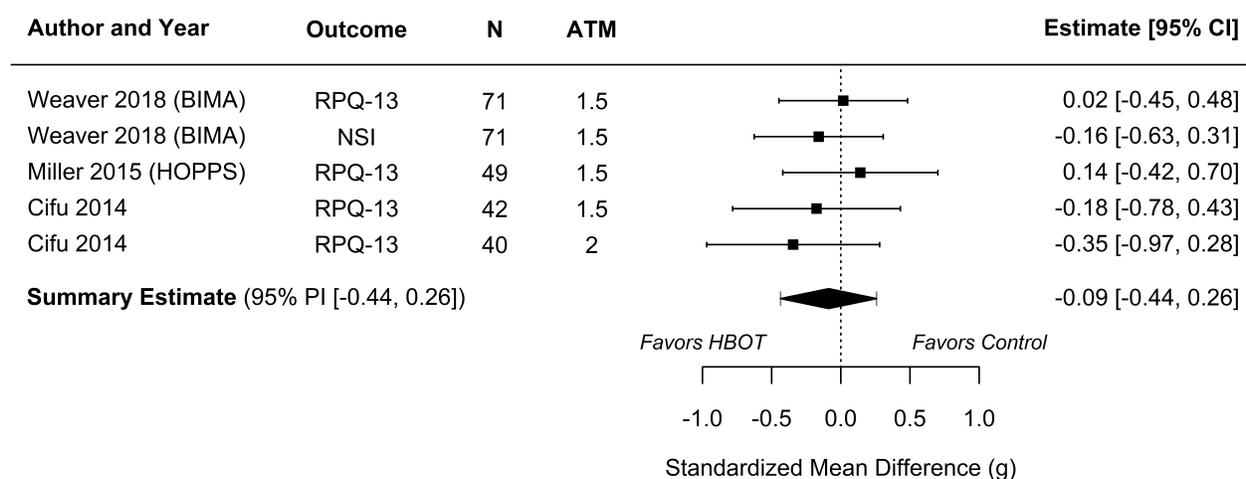
Mild TBI

Evidence from clinical trials of HBOT efficacy among patients with chronic mTBI was synthesized quantitatively. Results of meta-analyses of available post-treatment effects from sham-controlled trials, including the trial completed after the previous ESP review¹ (BIMA), are shown in Figure 3 (for post-concussion symptoms) and Figure 4 (for PTSD symptoms).

Overall, available evidence shows that HBOT does not lead to short-term improvements in post-concussion and PTSD symptoms among patients with chronic mTBI compared to sham. Synthesizing effect estimates from 3 sham-controlled RCTs,^{38,43,51} the overall post-treatment effect of HBOT on post-concussion symptoms (RPQ-13 and NSI) favored HBOT but was nonsignificant and very small ($g = -0.09$, 95% CI [-0.44, 0.26], $p = 0.83$), while for PTSD symptoms (PCL), the overall effect using evidence from 4 RCTs^{38,43,51,54} favored sham control (MD = 0.61, 95% CI [-7.75, 8.96], $p = 0.38$). Individual trial effects for both outcomes were also nonsignificant, inconsistent, and imprecisely estimated, as shown in Figures 3 and 4.

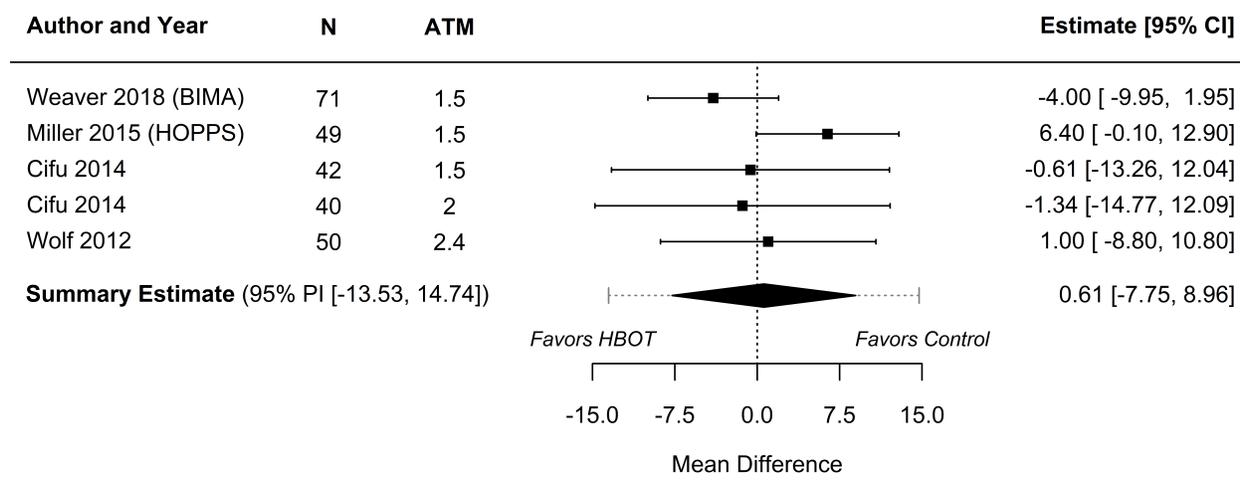
Sparse longer-term evidence suggests symptom improvement after HBOT is not durable. Longer-term effects on post-concussion symptoms, reported by 2 trials at 5.5 to 6 months from baseline and by 1 trial at 12 months from baseline, shared the same limitations as post-treatment effects. At 5.5 to 6 months,^{39,51} reported between-group differences in RPQ and NSI scores were nonsignificant and favored HBOT or neither group, while RPQ scores at 12 months favored control. Six- to 12-month effects on PTSD symptoms (PCL) were reported by only 1 sham-controlled trial⁵¹ and again were nonsignificant and inconsistent, favoring HBOT at 6 months and control at 12 months. The same trial also reported 24- and 36-month outcomes,⁴¹ but these results were only for a subset of original trial participants and were impacted by severe attrition. Reported confidence intervals for longer-term effects were wide and encompassed both improvement and worsening of symptoms relative to sham control.

Figure 3. Forest Plot of Standardized Mean Differences in Post-concussion Symptoms (RPQ-13 and NSI) from Sham-controlled Trials



Notes. Gray error bars around summary estimate diamond indicate 95% prediction interval (PI).

Abbreviations. ATA=atmospheres absolute, CI=95% confidence interval, HBOT=hyperbaric oxygen therapy, NSI=Neurobehavioral Symptom Inventory, PI=95% prediction interval, RPQ-13=Rivermead Post-concussion Symptom Questionnaire-13.

Figure 4. Forest Plot of Mean Differences in PTSD Symptoms (PCL) from Sham-controlled Trials

Notes. Gray error bars around summary estimate diamond indicate 95% prediction interval (PI).

Abbreviations. ATA=atmospheres absolute, CI=95% confidence interval, HBOT=hyperbaric oxygen therapy.

Several sham-controlled trials^{39,43,51,53} of active-duty military members with mTBI included patients with co-occurring mTBI and PTSD (range: 36-65%). Among these, 2 reported outcomes for PTSD subgroups adjusted for age and other covariates. Using uncorrected significance tests, the newly added trial⁵¹ found that post-concussion symptoms (RPQ-3) significantly favored HBOT immediately following treatment among participants with PTSD but not among those without PTSD. Improvements seen at 6 months (RPQ-3 and NSI) were nonsignificant, while symptoms did not differ or worsened compared to sham at 12 months. PTSD symptom (PCL) improvement in the PTSD subgroup favored HBOT post-treatment and at 6 months, but at 12 months results were nonsignificant and symptoms were again worsened compare to sham. The second trial,³⁹ which reported post-concussion outcomes (RPQ) 5.5 months from baseline, did not find evidence of moderation by PTSD status.

Results of a secondary analysis⁵⁰ of data from 2 of the above PTSD subgroups^{43,51} using a composite outcome (including cognitive, physical, and emotional symptoms and based on several existing measurement tools) reported similar findings, and a pooled analysis⁴¹ of included trials found that a PTSD status-by-intervention group interaction was nonsignificant. Finally, a subgroup analysis⁵⁷ (reported in an abstract only) of a previous trial⁵⁴ found that participants with an indication of PTSD (PCL-Military score of 50 or greater) were significantly more responsive to HBOT (2.4 ATA) than sham. Response was defined as a PCL score reduction of 10 or more points; however, baseline differences in absolute PCL scores between PTSD subgroups in treatment or sham conditions were not reported or accounted for in analyses (*ie*, PTSD-indicated patients in the HBOT group may have had higher PCL scores than PTSD-indicated patients in the sham group, and consequently responded more readily to intervention).

In the meta-analysis of post-concussion outcomes from sham-controlled trials, the similarity in prediction and confidence intervals (Figure 3) for the overall effect estimate suggests heterogeneity in effects between trials was minimal and most variation resulted from within-trial imprecision. In contrast, the prediction interval for PTSD symptoms (Figure 4) was larger than the confidence interval for the overall effect estimate, suggesting substantial heterogeneity in addition to imprecision within trials. Heterogeneity is likely due to the effects from the BIMA

and HOPPS trials, which were comparatively larger than other available effects and were in opposite directions.

Compared to sham-controlled trials, no-treatment or standard care-controlled trials^{40,43} observed effects that favored HBOT. Pooled effects, however, were nonsignificant for both post-concussion symptoms ($g = -1.51$, 95% CI [-18.96, 15.94], $p = 0.45$) and PTSD symptoms (MD = -7.41, 95% [-59.22, 44.41], $p = 0.33$). The only trial⁴⁰ completed since the previous ESP review¹ used a no treatment comparator and reported a large but imprecise effect in favor of HBOT. Comparisons to no treatment or standard care are vulnerable to biases associated with lack of blinding,^{27,28,58} and as a result, provide limited insight into HBOT efficacy. As discussed at length in our original review, the only trial⁴³ that included both a sham control group and a standard care control group suggests both HBOT and sham have similar effects, and both are superior to standard post-concussion care.

In addition to PTSD and post-concussion symptoms, several trials^{3,43,51} assessed whether HBOT led to improved patient quality of life. A crossover trial³ using a no treatment control condition found that patient quality of life (EQ-5D and EQ-VAS) improved following HBOT (among those assigned to receive HBOT and among control participants who received HBOT after crossing over). Two sham-controlled trials^{43,51} observed some post-treatment improvement in a number of health-related quality of life outcomes (SF-36) in both HBOT and control groups, but differences between groups were either nonsignificant or were not assessed for significance.

Moderate to Severe TBI

Seven previously reported RCTs^{24,36,42,44-47} examined the efficacy of HBOT (1.5, 2.0, or 2.5 ATA) for hospitalized patients with acute moderate to severe TBI. In 2^{46,47} of 4 trials reporting patient mortality following HBOT or standard neurosurgical care, HBOT led to significantly reduced patient mortality at 3 months to 1 year. In 3 trials^{24,42,44} comparing HBOT to standard care or medication therapy, improvement in coma severity (GCS) significantly favored HBOT (follow-up periods ranged from post-treatment to 6 months after treatment, or were not reported). Finally, 4 trials assessed changes in functional outcomes (GOS) after HBOT or standard care, and 2^{44,47} reported that improvement in functionality significantly favored HBOT at 6 to 12 months from baseline. A third trial⁴² reported improvement over standard care only among those with the highest functional rating at baseline (GOS-4), while a final trial⁴⁶ found that functional outcomes did not differ between groups. Several published meta-analyses, each including a subset of our included trials, generally agreed with these findings, reporting reduced mortality^{22,59} and coma severity^{21,22} with HBOT but conflicting evidence on improvement in functionality among patients with moderate to severe TBI.^{21,22,59} Importantly, in addition to variation in HBOT pressure, available trials differed in treatment frequency (1 or multiple daily sessions), session duration (30-120 minutes), and length of treatment course (3 days to 4 weeks).

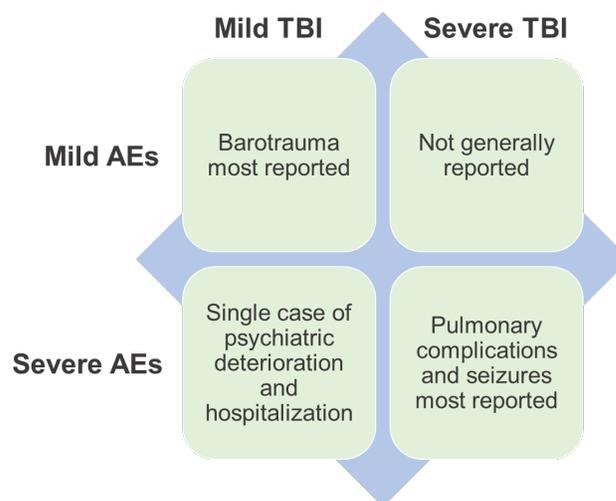
Unclear TBI Severity

A trial⁴⁸ that used a medication therapy control condition reported significant TBI symptom and function improvement following HBOT, but baseline TBI severity and outcome measurement details were not reported.

HARMS OR ADVERSE EVENTS OF HBOT FOR TBI WITH/WITHOUT PTSD

In most applications of HBOT, serious side effects are rare.⁶⁰ Among included trials of patients with chronic mTBI with/without PTSD, 5 reported on adverse events. Mild barotrauma (minor ear, sinus, or tooth pain or injury caused by pressurization) and headache appear to be the most common adverse effects of HBOT. In 2 trials,^{51,53} barotrauma was more frequently reported among HBOT group participants than sham group participants, but no other differences in adverse events between intervention groups were reported. Two trials^{3,37} reported participant withdrawal from the intervention due to minor adverse events (ear problems, claustrophobia, or headache). Only 1 trial⁴⁰ reported a serious event (psychiatric deterioration and hospitalization of a single patient).

Reporting of adverse effects among patients with severe TBI was carried out by 3 of 7 included trials. Two trials^{36,46} reported pulmonary complications among those receiving HBOT, and a previously published meta-analysis⁵⁹ of these trials found HBOT was associated with significantly increased risk of severe pulmonary complications compared to standard care (RR = 15.57, 95% CI [2.11, 114.72]; N = 228). Seizures were also reported with HBOT use in 2 trials (2 patients experienced seizures in each trial).^{42,46} Risk of seizure with HBOT use has been reported in other patient populations (eg, 0.3% of patients experienced seizures in a large retrospective cohort treated with HBOT for a wide variety of conditions⁶¹).



SUMMARY AND DISCUSSION

Findings of this updated synthesis align with those of the previous ESP report.¹ Updated findings include:

Acute TBI. For patients hospitalized with acute moderate to severe TBI, available evidence suggests HBOT can reduce mortality and coma severity more than standard neurosurgical care, but it is unclear whether HBOT improves longer-term functionality. Patients with acute severe TBI who receive HBOT may experience significant adverse effects, including severe pulmonary complications and seizures. Most HBOT trials in patients with acute TBI did not include current Service members or Veterans with blast-related TBI or patients with moderate TBI; therefore, evidence may be most applicable to patients with severe TBI from other causes.

Treating patients with acute moderate to severe TBI represents a considerably different clinical scenario than treatment of chronic mTBI (the most common form of TBI in Veterans⁶²) and prioritizes life-saving interventions typically delivered to hospitalized patients within hours or days of injury. In this application, evidence suggests HBOT may offer near-term benefits. However, because HBOT protocols varied widely across available trials and severe adverse effects may occur, clarity is needed on the protocol that optimally balances benefits and risks of HBOT for patients with acute moderate to severe TBI.

Chronic mTBI. When pooled, evidence on HBOT for chronic mTBI shows that HBOT does not lead to short-term improvements in post-concussion and PTSD symptoms compared to sham. Sparse longer-term evidence suggests symptom improvement after HBOT is not durable. HBOT appears to be well-tolerated by patients with chronic mTBI, with the most common side effect being mild barotrauma.

In several included sham-controlled trials,^{38,43,54} short-term symptom improvement was similar in both HBOT and sham groups, which suggests observed symptom change is likely the result of participation and/or placebo effects that occur because of the intensity of the HBOT intervention and its sham equivalent.^{43,63-65} Participation and placebo effects can result from the experience of accessing and receiving care (including sham treatment); engaging with and being engaged by providers, nurses, and other caring staff (for screening, intervention or sham delivery, and outcome assessment); and from patient and provider expectancies of treatment response.⁶⁵⁻⁶⁸

PTSD without TBI. Available evidence is not applicable to PTSD-diagnosed patients *without* a co-occurring TBI because no trials included these patients.

LIMITATIONS

Limitations of Included Trials

Design, measurement, and other methodological issues limit our confidence in the evidence on HBOT efficacy in patients with TBI with/without PTSD. First, trials of HBOT efficacy are generally small, leading to 2 concerns. Small RCTs are susceptible to prognostic imbalance, which occurs when there are unaccounted-for differences in factors that affect patient response to treatment across groups (that is, groups may be imbalanced in the likelihood that patients will improve over time).⁶⁹ Prognostic imbalance can be especially impactful when unadjusted analyses are used, as was often the case in included trials, and can lead to observed treatment

effects that are substantially larger or smaller than true treatment effects (or to observed effects when there are no true effects).⁷⁰ A second concern related to sample size is statistical power. Given their sample sizes, most included trials would not be able to detect effects smaller than $d = 0.7$ (a standardized difference in group outcome means at a nominal power of 0.80 and sample size of 60). Standardized mean differences in post-concussion and PTSD symptoms reported in included sham-controlled trials ranged in size from 0.02 to 0.36 (mean = 0.16). Consequently, it is likely that trials were generally underpowered to detect any true differences between HBOT and control groups of the magnitudes observed. This conclusion is corroborated by the frequently large reported p -values, which indicate low observed power.

Additionally, while existing HBOT trials have conducted baseline assessments, patient symptom and treatment histories were not longitudinally assessed *prior* to study enrollment. Without a clear picture of patients' preintervention symptom and treatment trajectories, important clinical variation in study samples may go unnoticed.^{1,71} If unaccounted for, this variation may lead to any true treatment effects of HBOT being artificially attenuated or exaggerated. Most trials also measured only mean changes in outcome scores, which may yield statistically significant findings, but the magnitude of the difference may not translate into a meaningful outcome for patients. Other methodological concerns include deviations from treatment protocols and lack of blinding of outcome assessors in some trials, and more broadly, methodological variation limited the ability to synthesize results of HBOT reported across trials. Trials varied in patient populations (timing of most recent TBI, length and characteristics of previous treatments, *etc*), HBOT protocols (chamber pressure, number and duration of sessions, *etc*), comparison groups (*eg*, inconsistent sham conditions, no treatment/standard care), and follow-up assessment timing.

Limitations of the Present Review

Limitations of our review methods include use of a second reviewer check during study selection, data abstraction, and quality assessment rather than dual independent review. Additionally, our search for measurement tools was not intended to be comprehensive, but instead focused on databases likely to contain high-quality systematic reviews for our targeted review of assessment measures for TBI and PTSD symptoms.

CONSIDERATIONS FOR FUTURE RESEARCH

Previous reviews^{1,71} have made suggestions for future sham-controlled efficacy trials that could address some limitations of the existing evidence on HBOT for treating chronic post-concussion symptoms. For example, because trials that randomize patients to HBOT and an inactive comparison condition are likely to have difficulty recruiting participants (participants are offered only a 50% chance of receiving active treatment), recommendations have included assigning a greater proportion of participants to treatment than to control conditions (*eg*, 80% to HBOT, 20% to sham); using a crossover design, in which all participants will ultimately receive treatment; or employing multiple treatment groups with different HBOT protocols (with a single, small sham group). Such designs could reduce patient resistance to enrolling by increasing the likelihood they would receive active treatment, and would maintain the benefits of a sham-controlled design (*ie*, patient blinding and the ability to detect potential participation effects). Trials using multiple treatment groups may offer other benefits, including clarifying any dose-response relationships associated with different HBOT pressurizations.

Although these alternative designs may improve some aspects of future HBOT efficacy trials, they are unlikely to address the lack of clinical applicability of traditional efficacy research (*ie*, trials that compare HBOT to an inactive control condition). These trials study HBOT as a standalone intervention rather than in a treatment context that aligns with VA/DoD guidelines for care of post-concussion symptoms, which recommend a coordinated stepped-care treatment approach incorporating multiple treatment modalities to address the wide array of symptoms attributed to concussion.^{18,65} Sham or no treatment comparison conditions also do not reflect typical clinical care options or the continuity of well-coordinated care. Consequently, comparisons between a standalone intervention and an inactive control do not provide a test of the real-world treatment value of the intervention (*ie*, versus or in addition to other available treatments that may be less resource intensive, less burdensome to patients, or more widely accessible).

Typically, health systems assign a low priority to treatments such as HBOT that have so far failed to show conclusive benefit over placebo, sham intervention, or usual care, and consider manufacturers and advocates to have the burden to prove that the intervention can work. While this is the case, it is important to recognize that a lack of effect when an intervention is compared to an inactive condition does not necessarily mean the intervention has no benefits. Indeed, it has been observed in many treatment contexts that an intervention and its placebo or sham equivalent generate a similar symptom improvement.⁷² When this occurs, a common (and correct) interpretation of the evidence is that the intervention is not superior to placebo (or sham), and often, the result of this judgment is the intervention is not taken up.

In this scenario, the observed symptom improvement is attributed to placebo and/or participation effects. In other words, it is characterized as a response to the *treatment ritual*,^{1,65} and not the treatment itself (*ie*, its purported biological mechanism). Effects resulting from the treatment ritual could be seen as suggesting the absence of “true” treatment effect, supporting a conclusion that an intervention is not efficacious. An alternative interpretation of effects arising from the treatment ritual is that some patients respond to the context of the intervention and the meaning of the intervention and its context.^{65,72} In this view, the psychological, interpersonal, and environmental features of a treatment ritual or process contribute to patient improvement, and should be identified and cultivated to increase benefit to the patient.⁷²

It is possible to evaluate evidence on HBOT in this framework. First, as described in the previous section, the pattern of symptom improvement in available trials strongly suggests participation and/or placebo effects: mTBI patients tended to improve to a similar degree immediately following HBOT *and* sham HBOT, and improved after HBOT more than after a period of standard care or no treatment. Second, HBOT and sham HBOT are accompanied by an elaborate treatment ritual that involves substantial patient effort, extensive engagement with providers and other patients, and regular access to treatment facilities and equipment. Third, because of the long duration of the HBOT intervention, this ritual is repeated among treatment and sham participants numerous times, leading to extensive exposure to an environment dedicated to improving the patient’s health. Taken together, then, the features of the intervention appear to be likely antecedents of the observed symptom improvement. What does not appear to be critical is the mechanism of the intervention itself, which in the case of HBOT and post-concussion symptoms, remains unclear.

For treatments with these characteristics, the question that follows is whether the lack of clarity on treatment mechanism and lack of benefit over placebo sufficiently justify disuse of the intervention. The question can also be reframed as *Does the observed benefit exceed the uncertainties?* If it does, subsequent questions involve the risk of harm of the intervention, and its costs and feasibility. The case of acupuncture for chronic pain is informative about these types of considerations. Although more evidence is available on acupuncture than HBOT, like HBOT, repeated trials have shown acupuncture *and* sham acupuncture produce demonstrable and similar symptom improvement, and shown that acupuncture leads to greater improvement than standard care.⁷³ At the same time, acupuncture has a poorly understood treatment mechanism, but is relatively low risk.^{73,74}

Acupuncture, which is a fairly low-resource intervention compared to HBOT, is now offered to Veterans despite little difference in effectiveness in sham-controlled trials and considerable controversy over negative results in some sham-controlled trials (debate focuses on the biological effects of various sham controls for acupuncture).⁷³ In practice, acupuncture is implemented consistent with its purported biological mechanism (*ie*, targeting anatomical points thought to facilitate healing), but is experientially indistinct from its sham equivalent. And, from the patient perspective, it is generally effective at improving the presenting symptoms – much like HBOT. Perhaps the most salient difference between HBOT and acupuncture is that HBOT is *not* low resource: It is a logistically complex intervention requiring dedicated treatment facilities, trained technicians and providers, and ongoing patient monitoring. This factor alone may limit implementation of HBOT, and from the policy-making perspective, decisions about whether additional research is warranted must consider whether patient, provider, and system resources required for HBOT would be better directed toward other approaches.

The hypothesis that the *features* of the HBOT therapeutic experience, not HBOT *per se*, lead to improved patient symptoms underlines that the therapeutic ritual is an important element of treatment, not necessarily an obstacle to it. These features – namely, the coordinated, long-duration engagement with caring providers and settings, high patient and provider expectancies for healing, and ongoing interaction with other patients with similar symptoms and experiences – are likely active components of the intervention.⁶⁵ Future research could examine the feasibility and benefits of incorporating these features into other treatment modalities for chronic post-concussion symptoms that are more widely implementable.

CONCLUSIONS

In hospitalized patients with acute moderate to severe TBI, available evidence suggests HBOT can reduce mortality and coma severity, but effects on longer-term functionality and the optimal HBOT protocol for acute TBI are unclear. Evidence on HBOT for chronic mTBI shows that HBOT does not lead to short-term improvements in post-concussion and PTSD symptoms compared to sham, and sparse longer-term evidence suggests symptom improvement after HBOT is not durable. At present there is no evidence from clinical trials about patients diagnosed to have PTSD *without* a co-occurring TBI. Decisions about whether additional research is warranted must consider whether patient, provider, and system resources required for HBOT would be better directed toward other approaches. One future research direction could be to examine whether features of the HBOT treatment experience (*eg*, coordinated engagement with providers and other patients) are themselves active intervention components that could be incorporated into more widely implementable treatments for chronic post-concussion symptoms.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA; contribute to the development of and approve final project scope and timeframe for completion; provide feedback on the draft report; and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix H in the supplemental materials for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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