



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

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Prepared by:

Evidence-based Synthesis Program (ESP)
Coordinating Center
Portland VA Health Care System
Portland, OR
Mark Helfand, MD, MPH, MS, Director

Investigators:

Kim Peterson, MS
Donald Bourne, MPH
Johanna Anderson, MPH
Erin Boundy, MS
Mark Helfand, MD, MS, MPH



PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. 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 ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

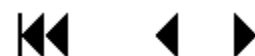
Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

Hyperbaric oxygen therapy (HBOT) is designed to increase the supply of oxygen to our blood and tissues and is thought to have osmotic and angiogenesis effects. In normal air, the oxygen level is only around 21% and the atmospheric absolute (ATA) pressure at sea level is 760 mmHg. HBOT delivers 100% medical grade oxygen inside a chamber where the air pressure is raised at least 1.4 times greater than normal. HBOT has been described as a high-tech, high-touch treatment that can require daily 2-hour sessions for 8 to 10 weeks in which participants are assisted by one or more specially-trained HBOT technicians and are sometimes accompanied by other patients in ‘multiplace’ chambers.

Following certain types of injuries, our bodies may demand more oxygen than is available in the normal air we breathe to supply our cells with the fuel necessary for healing processes (*eg*, metabolism, cellular growth and repair). The FDA has cleared HBOT, commonly at 100% oxygen delivered between 1.5 and 3.0 ATA, as a combination treatment of increased oxygen (hyperoxia) at increased hydrostatic pressure for several types of injury indications such as wound healing, necrotizing infections, burns, radiation injury, and carbon monoxide poisoning.

Given the microscopic and macroscopic wounds to the white matter of the brain that have been attributed to traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD), HBOT has also been explored as a therapy for these conditions. It has been used anywhere from between 3 to 71 months post-injury for mild TBI and within 24 hours for moderate to severe TBI. Among people who sustain mild TBI, up to 85% report persistent post-concussion symptoms (PPCS). Of those with PPCS, at least 90% have at least one co-occurring behavioral health condition, such as PTSD, and together these conditions have been labeled ‘post-deployment syndrome’. Among people with PPCS, mild TBI, PTSD, and post-deployment syndrome, many do not achieve remission with recommended treatments; thus, there remains a great need for innovative therapies.

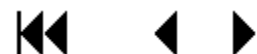
In case series of TBI and/or PTSD populations, HBOT, mostly at 1.5 ATA, has statistically significantly improved cerebral blood flow and mean scores on post-concussion symptoms (PCS), PTSD, depression, and anxiety symptom checklists, as well as cognitive functioning and quality of life. Statistically significant mean improvement on physiological outcomes and checklists does not always equal clinically significant symptom benefits. To best demonstrate a net benefit, ideally HBOT would significantly improve clinically significant symptom response, function, and quality of life over a control group in randomized controlled trials (RCTs) of patients with mild to severe TBI and/or PTSD, without increasing risk of serious harm.

Background

The ESP Coordinating Center (ESP CC) is responding to a request from the Center for Compassionate Innovation (CCI) for an evidence brief on the use of hyperbaric oxygen therapy (HBOT) for the treatment of traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), or their co-occurrence. Findings from this evidence brief will be used to inform considerations of clinical use of HBOT in Veterans with TBI and/or PTSD.

Methods

To identify studies, we searched MEDLINE®, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and other sources up to September 2017. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence.



Available RCT evidence on using HBOT for TBI and/or PTSD has been controversial, widely debated, and potentially confusing. Department of Veterans Affairs/Department of Defense (VA/DoD)-affiliated researchers, a 2015 US Government Accountability Office report, and a June 2017 independent systematic review have concluded that HBOT is no better than sham. HBOT proponents have raised concerns that (1) HBOT's lack of effectiveness is due to use of a mischaracterized sham in the control groups – shams that were not true shams, but were actually therapeutic treatments and (2) bias against HBOT in VA/DoD RCT investigators that has led to flaws in the design and interpretation of HBOT research. Our independent and objective re-analysis of 16 RCTs found inconclusive evidence of HBOT's benefits at least for mild TBI and PTSD, no obvious indication that bias led to flaws in VA/DoD RCTs, and that current evidence does not clearly support any one argument over another for or against HBOT.

For mild TBI, in the most recent fully published VA/DoD-funded RCT (HOPPS – ‘Hyperbaric Oxygen Therapy for Persistent Post-concussive Symptoms After Mild Traumatic Brain Injury’), neither HBOT at 1.5 ATA nor room air at 1.2 ATA (sham) significantly improved the proportion of military service members with a clinically relevant improvement in post-concussive symptoms after 8 to 10 weeks (≥ 2 -point improvement in Rivermead Post-Concussion Symptoms Questionnaire (RPQ—3)) compared to a no-chamber group – which an HBOT proponent described as the “only acceptable control group” (52% vs 33% vs 25%; $P=0.24$) because it lacks the potentially bioactive components of pressure and hyperoxia. Although this finding would seem to negate the ‘mischaracterized sham’ argument, we cannot rule out that the lack of improvement was due to a lack of adequate statistical power in the HOPPS RCT. Compared to sham (10.5% oxygen [O_2] at 2.0 ATA, room air at 1.2-1.3 ATA), HBOT given at 1.5 ATA or 2.4 ATA for mild TBI has also not significantly improved mean scores on other post-concussive symptom checklists or quality of life outcomes in other fully published VA/DoD RCTs. Although an Israeli civilian RCT had more positive findings, we have more doubt about its reliability due to its greater methodological limitations.

HBOT also did not significantly improve PTSD symptoms compared to sham in 2 VA/DoD RCTs with concomitant mild TBI and PTSD (mean difference in PTSD score change, -1.49 points, 95% CI -5.79 to 2.80), but interpretation of these findings is limited by imprecision, as only 37% to 65% of study participants had documented PTSD.

In patients with moderate to severe TBI, to best demonstrate a clinically important benefit over usual care, ideally (1) HBOT would significantly reduce risk of mortality, (2) improve the functional status and quality of life of the survivors, and (3) these benefits could be attributed specifically to HBOT and not between-group differences in the intensity level of medical care and decisions about life-sustaining treatment. Per the most recent and comprehensive systematic reviews, only one of these conditions has been met.

HBOT may increase risk of some serious harms when used in moderate to severe TBI. In patients with moderate to severe TBI, HBOT increased risk of severe pulmonary complications, but not seizures or ear barotrauma, compared to sham. In mild TBI, no serious adverse effects were reported and there were no significant differences between HBOT and control groups in specific adverse events

Proponents of HBOT for mild TBI and/or PTSD claim that the main confusion in interpreting the findings of HBOT RCTs is that the control groups of 1.2 to 1.3 ATA have been mischaracterized

as sham. Although the Hyperbaric Oxygen Committee of the Undersea and Hyperbaric Medical Society (UHMS) defines HBOT treatment pressure as at least 1.4 times higher than sea level, proponents of the ‘mischaracterized sham’ argument have suggested that lower pressures are actually active treatments with documented physiological and clinical effects. But the reliability of this claim is unclear because the documentation the proponents provide is not directly from patients with TBI and/or PTSD, but is from in vitro samples or patients with different conditions whose experiences with 1.2 to 1.3 ATA may or may not be comparable to TBI and/or PTSD, including chronic toxic encephalopathy, autism, cerebrovascular injury, epilepsy, or migraine.

Opponents claim HBOT has consistently shown no significant differences compared to sham, and thus is no more than a high-tech, high-touch ritual with “powerful nonspecific placebo effects”. We find 2 factors that preclude interpreting these findings as consistent evidence of no effect: (1) heterogeneity in HBOT protocol (1.5 ATA to 2.4 ATA), outcome assessment methods, timing (immediately following therapy, up to 6 weeks after discontinuation), and patient populations (most recent TBI ranged from 3 to 71 months) and (2) important methodological limitations.

In summary, the large treatment benefits demonstrated for HBOT in uncontrolled case series have not been easily replicated in well-controlled RCTs. Potential explanations for this include that the potential benefits are subtle and demonstration requires larger RCTs, HBOT is in fact ineffective, and/or the sham design has indeed been problematic. We disagree with both sides of the ongoing debate that the current evidence clearly points to one explanation over another. We simply still don’t know. Pooling data from the HOPPS trial and the yet unpublished BIMA trial – both of which compared HBOT 1.5 ATA to room air at 1.2 ATA, and used the RPQ to measure PCS symptoms – could shed light on the debate. Broad usage of HBOT as an initial treatment for mild or moderate to severe TBI and/or PTSD in lieu of conventional treatments still does not appear warranted. When patients do not respond to and/or do not tolerate adequate trials of multiple conventional therapy options and are considering emerging treatment options, offering HBOT to Veterans with mild or moderate to severe TBI and/or PTSD is reasonable. Prior to HBOT use, clinicians and patients should consider its potential increased risk of barotrauma and/or pulmonary complications. A small-scale clinical demonstration may provide the opportunity to improve data collection on comorbidities, clinically relevant patient outcomes, patient expectations, and documentation of the types and durations of previous and ongoing treatments.

EVIDENCE BRIEF

PURPOSE

The ESP Coordinating Center (ESP CC) is responding to a request from the Center for Compassionate Innovation (CCI) for an evidence brief on the use of hyperbaric oxygen therapy (HBOT) to treat Veterans with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) in whom other treatments have not been successful. Findings from this evidence brief will be used to inform considerations of clinical use of HBOT in Veterans with TBI and/or PTSD.

BACKGROUND

WHAT IS HBOT?

Hyperbaric oxygen therapy (HBOT) is designed to increase the supply of oxygen to our blood and tissues and is thought to have osmotic and angiogenesis effects. In the normal air we breathe, the level of oxygen is only around 21% and the atmospheric absolute (ATA) pressure at sea level is 760 mmHg. According to the Hyperbaric Oxygen Committee of the Undersea and Hyperbaric Medical Society (UHMS),¹ HBOT involves breathing 100% oxygen while inside a chamber where the air pressure is at least 1.4 times greater than normal.

Certain types of injuries that damage our cells, impair blood flow, and dysregulate our metabolism can result in a deficiency in the amount of oxygen reaching our tissues ('hypoxia'). Our bodies may demand more oxygen than is available in the normal air we breathe to supply our cells with the fuel for the necessary healing processes (*eg*, producing stem cells, inhibiting inflammation, reducing swelling, protecting cells from dying, promoting new blood vessel growth, regulating cellular metabolism, and promoting cellular growth and repair). The enhanced oxygen availability provided by HBOT has been associated with some of these healing mechanisms. As a medical device, hyperbaric chambers require 510(K) clearance from the United States Food & Drug Administration (FDA).² As of 2/1/18, HBOT - commonly delivered at 100% oxygen between 1.5 and 3.0 ATA, and defined as a combination treatment of increased oxygen (hyperoxia) at increased hydrostatic pressure - currently has 13 FDA-cleared indications, including treatment of air or gas embolism, carbon monoxide poisoning, decompression sickness ('the bends'), and soft tissue necrosis (see Appendix A in the supplemental materials for entire list) – none of which are PTSD or TBI.³

There are many types of hyperbaric chambers available that vary in features such as whether they are constructed of steel ('hard') or made of acrylic or urethane ('soft'), or accommodate only one patient ('monoplace') or more than one patient ('multiplace') at a time. HBOT chambers involve the use of medical-grade oxygen and are ideally operated by specially trained technicians who work under the supervision of a clinician.⁴ Depending on initial condition, tolerability of treatment, and treatment response, HBOT duration and frequency can vary from a few sessions to multiple sessions a day, 5 days a week, for 6 to 10 weeks. HBOT can be a highly social experience. Depending on the treatment plan, patients may have daily interactions with a team of nurses and hyperbaric technicians, and may interact with other participants in multiplace chambers.



WHY HBOT FOR TBI/PTSD?

Whether traumatic brain injury is mild or severe, patients can experience persistent and sometimes lifelong physical, cognitive, and emotional changes. Significant overlap exists among symptoms of TBI, persistent post-concussion symptoms (PPCS), and PTSD. In cases of moderate to severe TBI, defined as Glasgow Coma Scale (GCS) < 13 (plus normal or abnormal structural imaging, alteration of consciousness of > 24 hours, loss of consciousness of > 30 minutes, and posttraumatic amnesia of > 1 day), care is centered around life-saving measures as necessary, such as decompressive craniectomy, barbiturate administration, and seizure prophylaxis.⁵ However, mortality rates are still 19% to 36%⁶ and many survivors (> 50%) experience some degree of disability, cognitive impairment, behavioral changes, and are at increased risk for a multitude of neurological diseases that can result in moderate to severe functional impairment.^{7,8}

Among people who sustain a mild TBI (loss of consciousness of 0 to 30 minutes, normal structural imaging, alteration of consciousness, posttraumatic amnesia ≤ 24 hours, and GCS of 13 to 15), cognitive deficits in the first 2 weeks post-injury are common, but many recover within 30 days.⁹ However, many report persistent post-concussion symptoms (PPCS) including physical (*ie*, headache, dizziness, vision), cognitive (*ie*, memory, focus, judgment), and emotional (*ie*, depression, anger, anxiety) changes that last longer than 3 months following their injury and may take 6 months to a year to completely resolve.¹⁰⁻¹² Of those with PPCS, at least 90% have at least one co-occurring behavioral health condition such as depression, substance use disorder, or posttraumatic stress disorder, as well as chronic pain, sensory amplification, and medically unexplained symptoms, and together these conditions have been labeled ‘post-deployment multisymptom disorder’ or ‘post-deployment syndrome’.^{13,14} Reasons for lack of expected improvement can be complex and multidimensional, including failure to receive evidence-based interventions due to variability in clinician judgment and patients’ barriers to access and adherence, or presence of confounding prognostic factors, including medical and/or psychiatric comorbidities, premorbid personality traits, injury characteristics, biological and psychosocial factors, and/or inadequate psychoeducation.^{15,16} Many PPCS symptoms are similar to those of PTSD, and there is a high prevalence (50-80%) of PTSD among those diagnosed with PPCS or mild TBI.^{14,17} It has been hypothesized that neuronal damage following TBI may be involved in the development of neuropsychiatric disorders such as PTSD.¹⁷ In those with no history of physical head trauma, exposure to a life-threatening event or traumatic emotional experience can lead to abnormal activation of certain brain regions, such as the amygdala, which may also be involved in the development of PTSD. Discussion exists about the relationship between PTSD and TBI, whether PTSD-like symptoms in TBI should be classified as PTSD or a TBI symptom,¹⁸ or whether PTSD with and without a history of physical head trauma may have different mechanisms and/or should be classified as different subtypes (Appendix G – peer review disposition document).

Although the evidence base is limited,^{19,20} VA/DoD Clinical Practice Guidelines (VA/DoD CPG) for concussion-mild TBI recommend optimizing symptom improvement, functioning, well-being, and quality of life through a primary care, symptom-driven, personalized, and collaborative stepped-care approach including psychoeducation, cognitive rehabilitation, nonpharmacologic interventions such as sleep hygiene, education, dietary modification, physical therapy, relaxation, behavioral health treatments, and/or pharmacologic interventions (see Appendix B in supplemental materials for full list of related guidelines).²¹ VA/DoD guidelines

for PTSD recommend individual, manualized, trauma-focused psychotherapy over pharmacologic and other non-pharmacologic interventions as primary treatment.²²

Although some patients diagnosed with PPCS, mild TBI, PTSD, or post-deployment syndrome may not receive appropriate guideline-recommended treatments, among those that do, a large proportion have refractory symptoms, highlighting the great need for innovative treatments that can improve the health and well-being of this patient population. HBOT is one innovative treatment being explored for these difficult-to-treat conditions, given the potential for HBOT to promote healing of the microscopic and macroscopic wounds to the white matter of the brain that have been attributed to traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) (eg, shearing of axonal pathways and small blood vessels,²³⁻²⁵ including the common secondary injuries of cerebral hypoxia, increased cranial pressure, disruption of brain tissue and cellular metabolism, and inflammation).²⁶ In animal models of TBI, HBOT 1.5 ATA to 3 ATA has increased tissue oxygenation and neuronal stem cell proliferation and reduced inflammation, pressure in the brain and cellular death.²⁷ In TBI patients, HBOT 1.5 ATA to 2.5 ATA improved cerebral blood flow^{23,28} and glucose metabolism.²⁹ Gene array analyses have demonstrated positive impacts on gene expression.^{27,30}

DEBATE ON HBOT FOR TBI/PTSD

Although RCTs are available, HBOT for TBI and/or PTSD continues to be promoted largely based on case series and anecdotal testimonials. For example, in a few small military cohorts of 45 service members with chronic blast-induced mild to moderate TBI, PPCS, and PTSD, forty 60-minute sessions of HBOT 1.5 ATA resulted in 36% to 96% increases in perceived quality of life and percentage back to normal cognitive, physical, and emotional function reported.^{28,31} There are also many testimonials and anecdotal reports of HBOT as a “miracle cure” for TBI and/or PTSD that is “giving people back their lives.”^{32,33} Based on such anecdotal reports, HBOT has gained some political advocacy, such as from Congressman Walter B. Jones in North Carolina and other lawmakers, which has resulted in Oklahoma, Texas, and Indiana passing legislation establishing funding to provide eligible Veterans with TBI and/or PTSD with access to HBOT.³⁴ To address anecdotal reports, on 8/22/2013 FDA issued a Consumer Update statement that “HBOT has not, however, been proven to be the kind of universal treatment it has been touted to be on some internet sites” and listed brain injury as one of the conditions for which “the safety and effectiveness of HBOT has not been established.”³⁵

Available RCT evidence on using HBOT for TBI and/or PTSD has been controversial, widely debated, and potentially confusing. Skeptics have described HBOT as no more than a high-tech, high-touch ritual³⁶ with “powerful nonspecific placebo effects”³⁷ due to the “act of engaging in daily HBO treatment sessions for more than one month,”³⁷ that is often accompanied by “greatly reduced duty schedules” and “enhanced access to leisure time.”²⁴ HBOT for TBI and/or PTSD has not yet been endorsed for broad use or coverage in practice guidelines and payer policies (Appendix B).

Proponents of HBOT have stated that the main confusion in interpreting the findings of HBOT RCTs is that the control groups of 1.2 to 1.3 ATA have been mischaracterized as “sham”, when they are actually active treatments that are effective in their own rights. The suggestion that the low-pressure control groups are therapeutic is based on the premise that the slight increase in air pressure and/or the minor increases in oxygen partial pressure are biologically and

physiologically active.^{38,39} HBOT proponents have also raised concerns about bias against HBOT in VA/DoD RCT investigators that has led to flaws in the design and interpretation of HBOT research.⁴⁰⁻⁴⁶

CONSIDERATIONS FOR EVALUATING HBOT AS AN EMERGING TREATMENT FOR TBI/PTSD

The high prevalence and burden of TBI and/or PTSD combined with the lack of broadly effective treatments has created a definite need to identify additional therapeutic options. If the types of clinical ritualistic components that characterize HBOT are of interest (*ie*, high-tech, high-touch, mental break), other innovative treatments for TBI and/or PTSD that might be reasonable to explore or to compare HBOT to include HBNO₂ (mild hyperbaric pressure of 1.3 ATA and regular air) and float therapy. For example, with float therapy, also known as sensory deprivation and restricted environmental stimulus therapy (REST), people can experience a “nearly 100 percent stimuli-free environment” by effortlessly floating in a futuristic pod filled with 150 gallons of skin temperature water and 1,000 pounds of Epsom salt where there is absolutely no light and sound and all “routine environmental and physical stimulation, such as light, sound, and gravity” are removed.^{47,48} The theory behind REST is that the sensory deprivation could stimulate reparative synaptic changes in the brain (‘rewiring’ or ‘neuroplasticity’) and some preliminary functional MRI case reports have shown REST has increased activity in brain regions commonly affected by TBI.⁴⁷ Also, some have suggested exploring the use of regular air delivered at mild hyperbaric pressure of 1.3 ATA (HBNO₂), as it has shown some clinical improvement and is “significantly less expensive and logistically simpler treatment” than HBOT.²³

Regardless of the innovative intervention, to best assess the impact, the ideal evidence would include individuals with well-documented TBI and/or PTSD, would document their existing comorbidities and baseline severity and duration of symptoms, and would evaluate the treatment effects on clinically important benefits as recommended by the VA/DoD CPG (including functioning, well-being, and quality of life). At least for HBOT, to help add meaning to why any such improvements occur, and potentially shed light on the sham debate, clinical evaluation should be done in tandem with neuroimaging and assessment of the role of potentially exaggerated patient expectations that may have resulted due to publicized reports of HBOT as a “miracle cure”. As any positive effects of HBOT should not come at the expense of increased risk of serious harm, assessment of the adverse effects of HBOT is also important. To best assess the generalizability of available evidence on HBOT to Veterans with TBI and/or PTSD in whom other treatments have been unsuccessful, ideally the types and durations of previous and ongoing treatments would be well-documented.

The aim of this evidence brief is to evaluate the potential impact of HBOT on TBI and/or PTSD on certain clinically important benefits and harms and evaluate whether they differ based on patient characteristics and variation in HBOT protocol.

SCOPE

Objective: To synthesize the evidence regarding the potential benefits and risks of hyperbaric oxygen therapy (HBOT) for traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), or their co-occurrence.

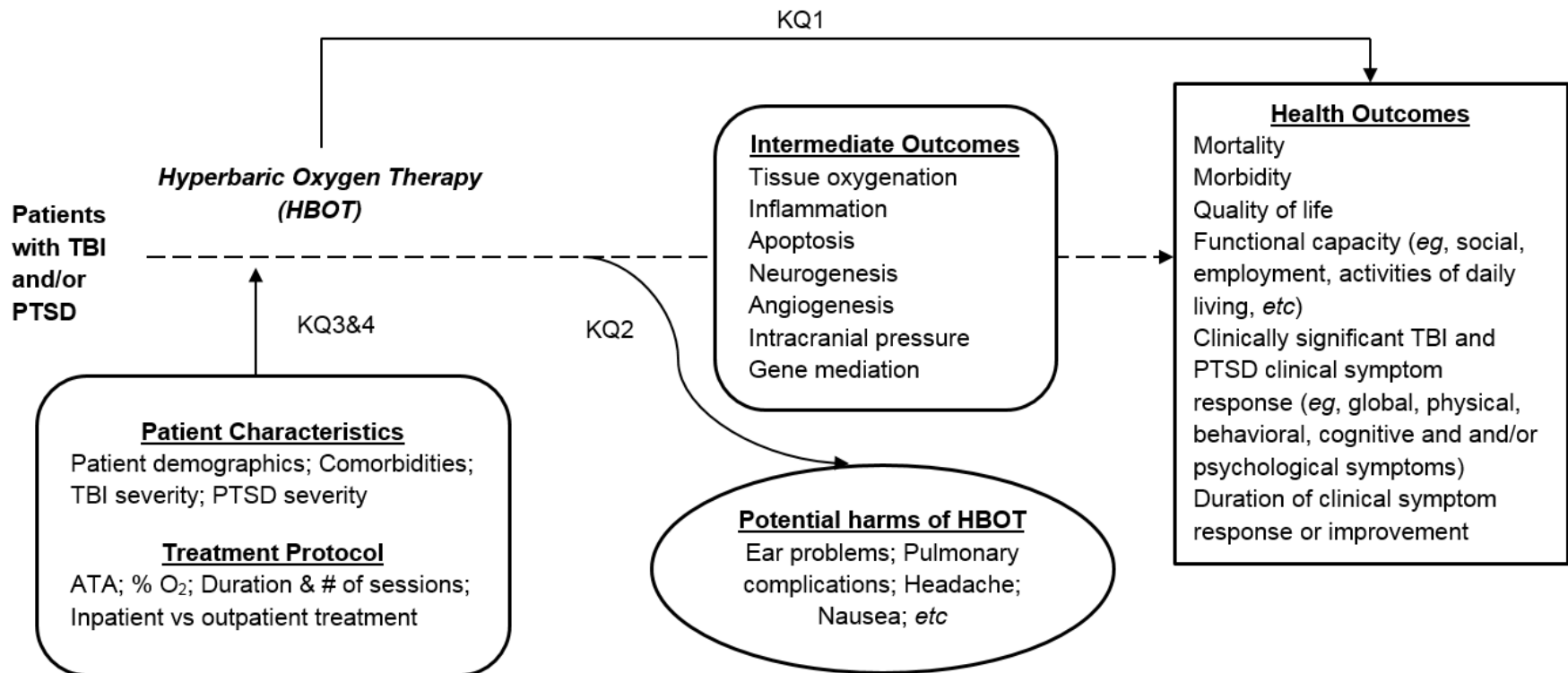
KEY QUESTIONS

- 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 below (Figure 1) illustrates the Population, Interventions, Comparators, Outcomes, Timing, Setting, and Study designs (PICOTSS) of interest that guided this review and their relationship to the key questions. This evidence brief addresses the evidence evaluating the direct link between HBOT and health and clinically significant outcomes (Key Question 1) and potential risks (Key Question 2). Key Questions 3 and 4 examines whether the benefits and/or risks of HBOT differ per patient characteristics (*eg*, patient demographics, comorbidities, disease severity) or per treatment protocol (*eg*, number of sessions, amount of pressure, inpatient vs outpatient treatment).

Figure 1. Analytic Framework



ELIGIBILITY CRITERIA

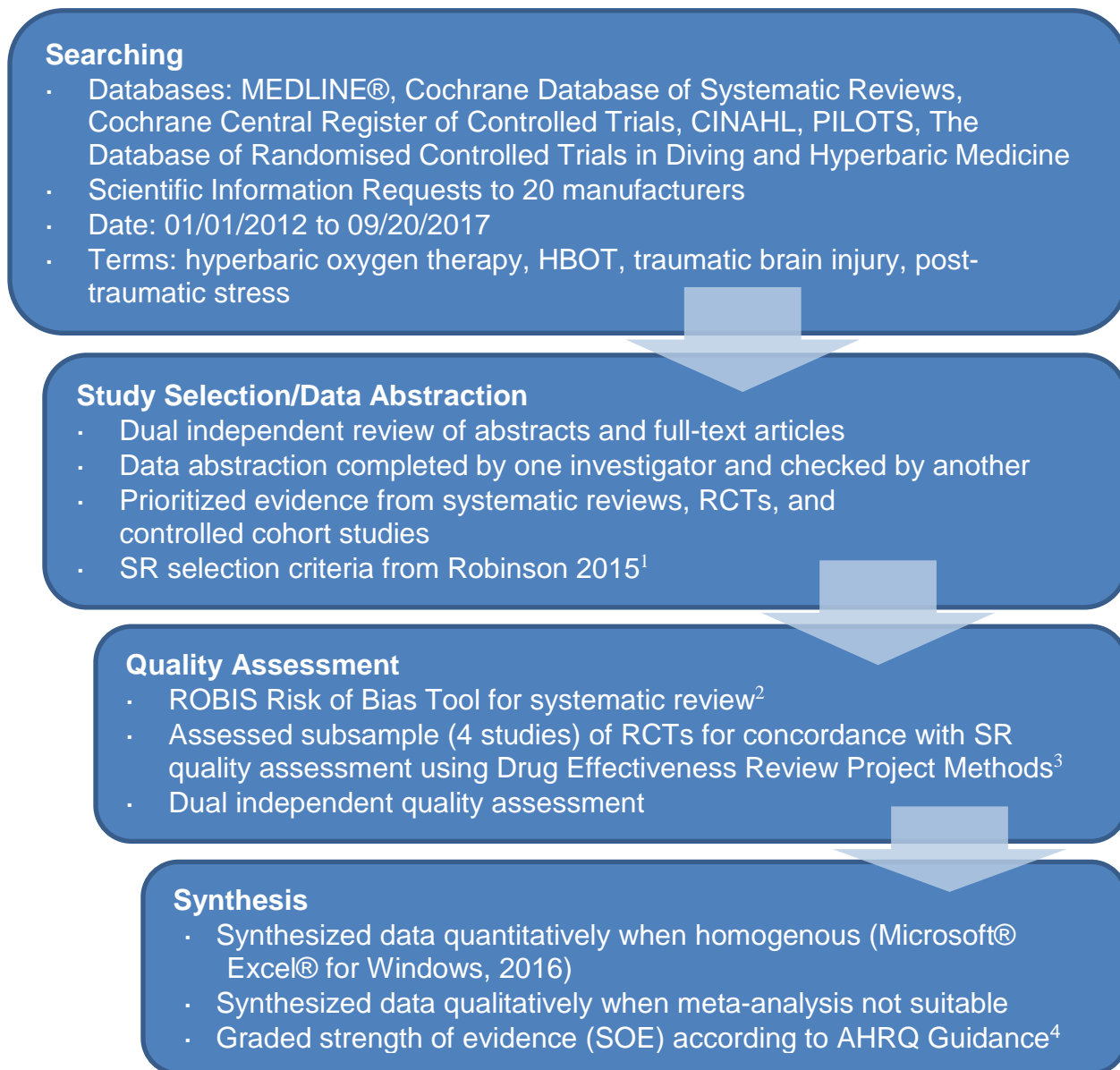
The ESP included studies that met the following criteria:

- **Population:** Patients with TBI, PTSD, or the co-occurrence of TBI and PTSD
- **Intervention:** HBOT, any protocol
- **Comparator:** Any. Regardless of the debate over whether or not the comparator groups of room air at < 1.5 ATA have been mischaracterized as ‘sham’ and are actually a therapeutic dose of HBOT (described above), for the sake of describing the included study results, we will refer to them as sham.
- **Outcomes:**
 - **Benefits:** Mortality, morbidity, quality of life, functional capacity (*eg*, social, employment, activities of daily living, *etc*), clinically significant TBI and PTSD clinical symptom response (*eg*, global, physical, behavioral, cognitive and and/or psychological symptoms), and duration of clinical symptom response or improvement. An example of clinically significant clinical symptom response is the proportion of patients with ≥ 2 -point change in Rivermead Post-Concussion Symptoms Questionnaire. We will accept any definition of clinically significant clinical symptom response. We will consider measures of mean change in clinical symptoms to address gaps in clinical response measures. We will exclude intermediate physiologic measures, such as intracranial pressure, cerebrospinal fluid lactate levels, or changes in cerebral blood flow that patients may not subjectively experience.
 - **Harms:** Any (ear problems, pulmonary complications, headache, nausea, *etc*)
- **Timing:** Any
- **Setting:** Any
- **Study design:** Systematic reviews (prioritized based on Robinson et al⁴⁹), randomized controlled trials, and concurrently controlled cohort studies. We will consider case series (N>1) only to address gaps in evidence from studies with control groups. We will exclude case reports (N=1).

METHODS

We followed the steps in the systematic review process outlined below. For complete search strategies, see Appendix C in supplemental materials. A draft version of this report was reviewed by peer reviewers as well as clinical leadership. Their comments and our responses are presented in the Supplemental Materials, Appendix G.

Figure 2. Review Methods



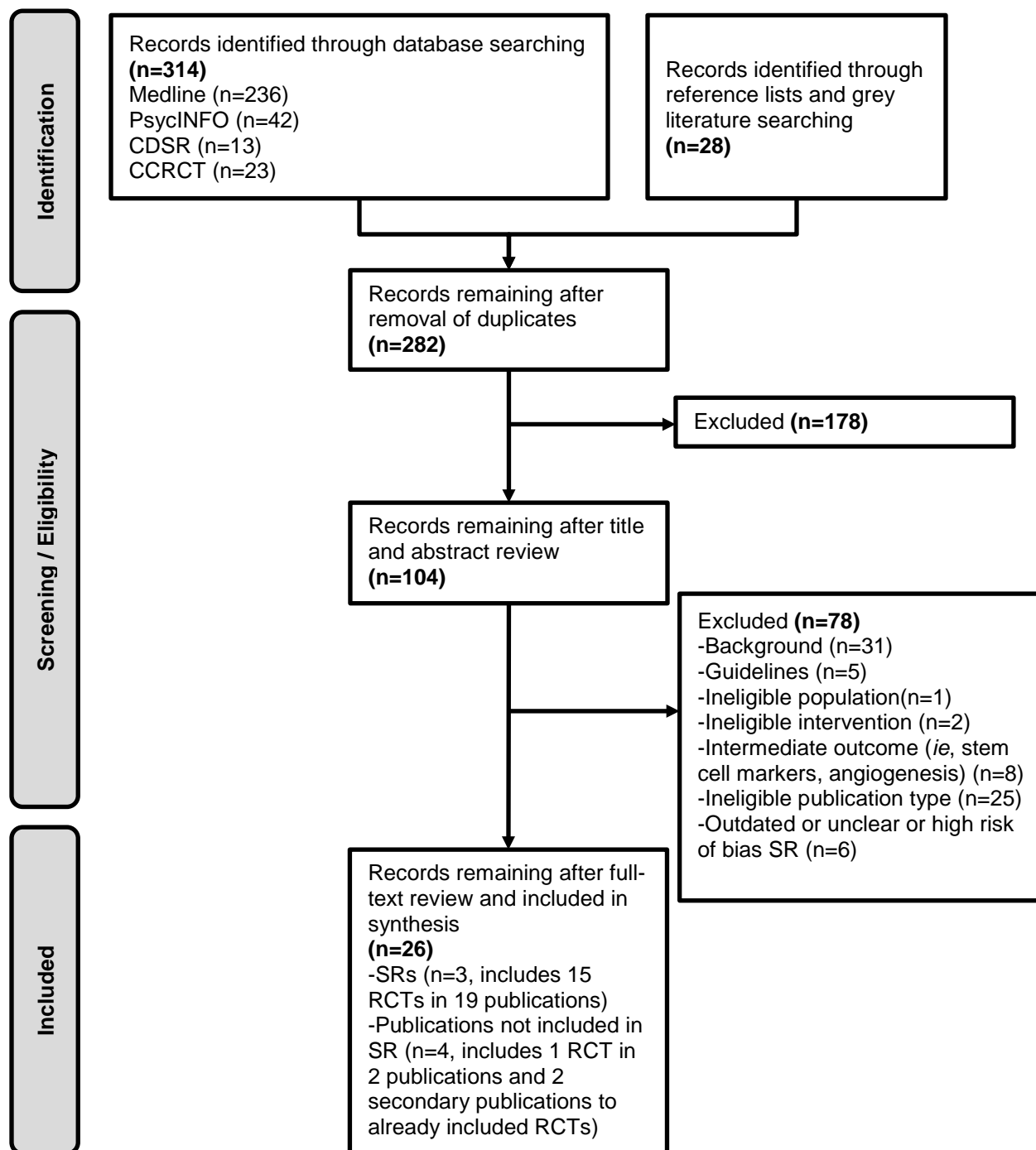
1: Robinson et al. Twelve recommendations for integrating existing systematic reviews into new reviews: EPC guidance. *J Clin Epidemiol.* 2016; **2:** Whiting et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol.* 2016; **3:** McDonagh et al. Methods for the drug effectiveness review project. *BMC Med Res Methodol.* 2012; **4:** Berkman et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: Agency for Healthcare Research and Quality;2013.

RESULTS

The literature flow diagram (Figure 1) summarizes the results of the search and study selection processes. See Appendix D in supplemental materials for full list of excluded studies.

LITERATURE FLOW

Figure 3: Literature Flowchart



LITERATURE OVERVIEW

Our search identified 282 unique, potentially relevant articles. We included 3 good-quality systematic reviews^{26,50,51} which included 15 RCTs (in 19 publications),^{23-25,29,52-68} and one subsequently published RCT (in 4 publications),^{69,70} for a total of 26 publications (Table 1; see supplemental materials Appendix E for full evidence tables). Five RCTs^{23-25,53-55,63,66,67,69,70} reported outcomes for patients with mild TBI with or without PTSD, 10 RCTs^{29,52,57-62,64,65,68} reported outcomes for patients with moderate to severe TBI, and 1 RCT⁵⁶ failed to report on TBI severity. No studies focused exclusively on patients with PTSD or separately analyzed PTSD subgroups, and the prevalence of PTSD in these studies was 36%⁶⁶ to 65%.⁶³ The majority of studies were in mostly male populations with a mean age range from 20 to 44 years. The number of HBOT sessions ranged from 3 to 84 and exposure lasted from 1 to 2 hours. We generally concurred with the ratings from previous systematic reviews that most studies had ‘few’ or acceptable levels of methodological limitations. The majority of RCTs were short-term (≤ 10 weeks) and none evaluated durability of effects.

We identified one potentially relevant study on mild TBI (BIMA) that is pending publication, and additional ongoing studies (see Appendix F in supplemental materials for details).⁷¹ None of the ongoing studies are expected to address important gaps in the literature. We sent requests for scientific information to 20 HBOT chamber manufacturers to identify additional published, unpublished, and supplemental data on published studies, but did not receive any submissions.

Table 1: Characteristics of Included Studies

Population	Evidence	Patient Characteristics	HBOT Characteristics	Sham Characteristics	Methodological limitations
Mild TBI with or without PTSD	5 RCTs ^{23-25,53-55,63,66,67,69,70} N= 320	Service members or Veterans: 0 to 100% % male: 39 to 100% Mean age range: 21 to 53 years Time from TBI to HBOT initiation: 3 to 71 months	# sessions: 30 to 40 Exposure: 60 to 117 minutes Duration: 8 to 12 weeks ATA: 1.3 to 2.4 % O ₂ : 100%	# RCTs with sham: 3 ^{24,25,53-55,63,66,67,69,70} # sessions: 30 to 40 Exposure: 60 to 117 minutes Duration: 8 to 12 weeks ATA: 1.2 to 1.3 % O ₂ : 10.5 to 75%	4/5 had few* or acceptable [†] _{50,51} 1/5 not assessed ^{69,70}
Moderate to severe TBI	10 RCTs ^{29,52,57-62,64,65,68} N= 747	Service members or Veterans: 0% % male: 62 to 100%	# sessions: 3 to 84 Exposure: 40 to 120 minutes Duration: 3 to 52 days	# RCTs with sham: 1 ⁵⁷ # sessions: 3 Exposure: 180 minutes Duration: 3 days	6/10 had few* or acceptable [†] _{50,51} 3/10 had few [†] ₅₁

Mean age range: 23 to 40 years	ATA: 1.5 to 2.55 % O ₂ : 100%	ATA: 1.0 % O ₂ : 100 %	1/10 had unacceptable levels* ²⁶
Time from TBI to HBOT initiation: ASAP, ≤24 hours to 10 days			

*Cochrane Collaboration's Risk Assessment Tool

† SIGN 50 tool

One RCT⁵⁶ did not report TBI severity was omitted from this table.

Abbreviations: ATA=atmosphere absolute (pressure), ASAP=as soon as possible, HBOT=hyperbaric oxygen therapy, O₂=oxygen, TBI=traumatic brain injury, SIGN= Scottish Intercollegiate Guidelines Network

KQ1: WHAT ARE THE POTENTIAL BENEFITS OF HBOT FOR THE TREATMENT OF TBI AND/OR PTSD?

Mild TBI

The 39% to 96% increase in perceived quality of life and percentage back to normal cognitive, physical, and emotional function reported in case series²⁸ have not been easily replicated in the most well-controlled RCTs with the greatest relevance to Veterans, which were conducted by the VA/DoD (Table 2). HBOT has not significantly led to a clinically important improvement in TBI and/or PTSD symptoms, function, or quality of life compared to an adequate control group, and RCTs have not shown that any such improvements are durable beyond the few weeks following therapy discontinuation.^{23-25,63} Neither has HBOT been shown to be consistently ineffective. Although HBOT given at 1.5 ATA to 2.4 ATA generally did not significantly improve post-concussive symptom or quality of life outcomes compared to control groups of 1.2-1.3 ATA in the 3 published VA/DoD RCTs, heterogeneity in HBOT protocol (1.5 ATA to 2.4 ATA), outcome assessment methods and timing (immediately following therapy, up to 6 weeks after discontinuation), and patient populations (most recent TBI ranged from 3 to 71 months), and important methodological limitations preclude interpreting findings as consistent evidence of no effect. Although an Israeli civilian RCT had more positive findings, we have more doubt about its reliability due to its greater methodological limitations.

VA/DOD Studies

Four VA/DoD RCTs have compared HBOT to conditions characterized as sham in which room air was delivered at low-pressure ATA (1.2 to 1.3)^{25,63,71} or low oxygen (10.5%) was delivered at 2.0 ATA²⁴ to simulate “middle ear pressure effects and adiabatic heating and cooling effects of pressurization and depressurization”. In the most recent fully published DoD-funded RCT (HOPPS), neither HBOT 1.5 ATA nor room air at 1.2 ATA (sham) significantly improved the proportion of military service members with a clinically relevant improvement in post-concussive symptoms after 8 to 10 weeks (≥ 2 -point improvement in Rivermead Post-Concussion Symptoms Questionnaire (RPQ—3)) compared to a no-chamber group – which an HBOT proponent described as the “only acceptable control group because it is the only control group which lacks the potential bioactive components of pressure and hyperoxia”⁷² (52% vs 33% vs 25%; $P=0.24$). Although this finding would seem to negate the ‘mischaracterized sham’ argument, we cannot rule out that the lack of improvement was due to a lack of adequate statistical power in the HOPPS RCT. Although this study required 72 patients for adequate

statistical power, only 64 were included in their analysis. No significant differences between HBOT, low-pressure, and no-chamber groups were found in various quality of life SF-36 subscales, but results generally favored the low-pressure group over the HBOT group. Otherwise, compared to the low-pressure 1.2 to 1.3 ATA control groups in the other VA/DoD RCTs, HBOT significantly improved post-concussion symptoms only when delivered as 100% oxygen at 1.5 ATA, as described in the most recent VA/DoD RCT, which has not yet been fully published in a peer-reviewed journal (BIMA, Brain Injury and Mechanisms of Action study).⁷¹ According to the RPQ-3 2-point threshold used in the Miller 2015 RCT, though, this 1.5 difference in BIMA, while statistically significant, may not be clinically relevant. In the 3 other VA/DoD RCTs,^{24,25,63} 1.5 ATA, 2.0 ATA, and 2.4 ATA HBOT did not significantly improve PCS symptom response or quality of life. Factors including (1) heterogeneity in HBOT protocol (1.5 ATA to 2.4 ATA), outcome assessment methods and timing (immediately following therapy, up to 6 weeks after discontinuation), and patient populations (most recent TBI ranged from 3 to 71 months), and (2) important methodological limitations preclude interpreting these findings as consistent evidence of no effect. Also, the generalizability of the VA/DoD RCT findings to Veteran population is unclear, as the majority of participants in the VA/DoD studies were active-duty service members who were receiving paid travel, greatly reduced duty schedules, and enhanced access to leisure time during their participation in the RCTs.²⁴

Perhaps most important is that HBOT still lacks evidence from RCTs on the durability of its potential benefits. HBOT's improvements in the RPQ-3 compared with sham in the unpublished BIMA have been reported to "regress" at 6 and 12 months.⁷¹

Israeli Civilian RCT

HBOT has shown promise in Israeli civilians at the late chronic stage of mild TBI (mean of 33 months post-injury) after a protocol of 40 sessions, 5 days a week, 60 minutes each, with 100% oxygen at 1.5 ATA.²³ This HBOT protocol improved quality of life compared to a control group of 'no treatment' (-17.7% vs +4.7%; P =not reported; baseline = 7.70 to 7.87 on European Quality of Life-5 Dimensions (EQ-5D), score of 5 = no problems; score 25 = extreme difficulties).²³ This same HBOT protocol also improved quality of life in the 'no treatment' control group when they crossed over to HBOT (-16.3% vs +4.7%; P =not reported). While encouraging, this RCT has several methodological limitations, the greatest of which is that we can't rule out the 'participation effect', as the only comparison was to an unblinded, no-treatment control group. Second, this is a single, underpowered study. The number of patients analyzed in the control group was lower than the $N=31$ needed to detect a 10% or greater improvement on the neurocognitive test score, and it is unclear how that power calculation applies to the EQ-5D. Finally, the analysis excluded more patients in the control group overall (22% vs 11%), the majority of which were due to "technical performance problems in their cognitive tests" (16% vs 5%), which could have been related to poorer neurocognitive and quality of life outcomes. Additionally, the applicability of the findings from these studies to Veterans with mild TBI is unclear because this study included 57% women with a higher mean age than the VA/DoD populations, and the comparability of the potential cumulative effects of multiple TBIs, their concomitant secondary diagnoses (*ie*, PTSD), or other previous or concurrent TBI treatment are unknown because they were not reported.

Table 2. Post-concussive Symptom and Quality of Life Outcomes for HBOT versus Sham in VA/DoD RCTs

Author Year Size	Time of most recent TBI occurrence before randomization	% with PTSD	HBOT protocol	Sham protocol	Post-concussive symptom outcomes	QOL outcomes	Comments
Wolf 2012-2015 ^{25,35,53,54} N=50	NR, range of 3-71 months	Mean baseline PCL-M: 49-50 pts	100% O ₂ at 2.4 ATA	Room air at 1.3 ATA	PCL-M composite mean score at baseline/6 weeks post-exposure/change: 50.0/41.6/-8.4 vs 48.9/40.6/-8.3 (<i>P</i> =0.28)	NR	Highest dose; possible “overdose” Outcomes measured 6 weeks after completion
Cifu/Walker 2014 ^{24,55,66,67,73} N=60	8.5 months	% with PCL ≥ 50 pts: 36.5%	75% O ₂ at 2.0 ATA (1.5 ATA equivalent), 100% O ₂ at 2.0 ATA (2.0 ATA equivalent)	10.5% O ₂ at 2.0 ATA	RPQ total score pre/post-compression/change [†] for 1.5 ATA vs 2.0 ATA vs sham: 29.33/30.57/+1.24 vs 30.44/26.67/-3.77 vs 32.81/32.86/+0.05; <i>P</i> =0.19 for post-compression	NR	Most recent TBI Unique protocol of 2.0 ATA for all groups and varying O ₂ levels
Miller 2015 ⁶³ N=72	23 months	65%	100% O ₂ at 1.5 ATA	Room air at 1.2 ATA; no chamber	% patients ≥ 2-pt RPQ-3 improvement for HBOT vs sham vs no chamber: 52% vs 33% vs 25%; <i>P</i> =0.24	SF-36: Results favored <i>sham</i> on 7 of 8 domains	Underpowered; needed 72, only evaluated 64
Weaver 2016 / 2017 ^{*70,71} N=71	Mean NR, 72% were 1-5 years from their most recent TBI	49%	100% O ₂ at 1.5 ATA	Room air at 1.2 ATA	RPQ-3 mean change difference: -1.5, <i>P</i> =0.01	NR	Unpublished

*Conference Proceeding

†EPC-calculated: increase=worsening, decrease=improvement

Abbreviations: ATA=atmosphere absolute, PCL-M=Post-traumatic Disorder Check List-Military Version, O₂=oxygen, RPQ-3=Rivermead Post-Concussion Symptoms Questionnaire-3 subscale, SF-36=(Rand) 36-Item Short Form Health Survey, TBI=traumatic brain injury



Moderate to Severe TBI

In patients with moderate to severe TBI, to best demonstrate a clinically important benefit over usual care, ideally (1) HBOT would significantly reduce risk of mortality, (2) improve the functional status and quality of life of the survivors, and (3) these benefits could be attributed specifically to HBOT and not between-group differences in the intensity level of medical care and decisions about life-sustaining treatment. According to the 3 good-quality systematic reviews, only one of these conditions has been met.^{26,50,51} HBOT (1.5 to 2.55 ATA) consistently reduced odds of death in 2 meta-analyses.^{26,50} HBOT reduced the relative risk of mortality in the earlier meta-analysis of 3 RCTs published between 1974 and 1992 (0.69, 95% CI 0.54 to 0.88, $P = 0.003$).²⁶ In the 2016 review by Wang et al of 3 newer RCTs published between 1992 and 2013, HBOT reduced the odds of mortality by 68% (OR=0.32, 95% CI 0.18 to 0.57)⁵⁰ and improved Glasgow Coma Scale (GOS) by 278% (OR=3.78, 95% CI 1.23 to 11.63) compared to the control groups based on 3 overall good-quality RCTs.⁵⁰ The GOS improvement was driven by a single study⁶⁵ performed in China with a control group where the mortality rate was almost double that observed in other included studies.⁵⁰ A sensitivity analysis after removal of this study⁶⁵ found no significant difference in GOS improvement (OR [random effects]=2.18, 95% CI 0.92 to 5.17).⁵⁰

The applicability of these results to Veterans is likely low because none of these studies included current service members or Veterans or those with blast-induced TBI. Furthermore, the majority of TBIs in Veterans are mild – moderate to severe TBIs only make up 9.4% and 1.1%, respectively, of TBIs sustained by service members since 2000.⁷⁴

PTSD

Little is known about the benefits of HBOT in patients with PTSD. While no studies focused exclusively on patients with PTSD, several studies included patients with concomitant TBI and PTSD. None of these studies did a responder analysis of clinically important PTSD improvements. A meta-analysis of the 2 RCTs^{24,25,53,66,67} by Cifu et al and Wolf et al that reported complete pre- and post-treatment PTSD score data showed no significant difference in PTSD score change between HBOT and control groups (pooled difference in means (fixed effects) = -1.45, 95% CI -5.79 to 2.80).⁵⁰ The applicability of these findings to patients with PTSD is unclear because the prevalence of PTSD in these studies was only 36%⁶⁶ to 65%⁶³ and PTSD subgroups were not separately analyzed. HBOT also did not significantly improve PTSD symptoms compared to sham in the most recent HOPPS trial, which was not included in the meta-analysis.⁶³

KQ2: WHAT ARE THE POTENTIAL RISKS OF USING HBOT FOR THE TREATMENT OF TBI AND/OR PTSD?

Minor ear problems, such as ear pain and barotrauma, appear to be the most common adverse effects of HBOT. Serious harms of HBOT appear limited to use in moderate to severe TBI, in which HBOT increased risk of severe pulmonary complications, but not seizures or ear barotrauma. In mild TBI, no serious adverse effects were reported and there were no significant differences between HBOT and control groups in specific adverse events. Substantial uncertainty remains, as evidence was likely underpowered to detect serious but rare adverse effects.

In mild TBI, HBOT did not lead to any serious adverse events and there were no significant differences in withdrawals due to adverse events compared with sham (2% vs 2%). There was a numerically higher rate of ear barotrauma for HBOT compared to sham when given at higher dosages (42% vs 16%, $P = 0.57$ at 2.4 ATA for 90-minute sessions,⁵⁴ 8% vs 0% at 1.5 ATA for 60-minute sessions⁶³), but the difference was not statistically significant. The second most common adverse event was headache, reported in 4 HBOT patients (16.7%) and 3 sham patients (12.5%).⁶³ Only 2 of 4 mild TBI studies, involving only 95 participants, reported harms.^{25,53,54,63}

In moderate to severe TBI, HBOT significantly increased risk of severe pulmonary complications (13% vs 0%, RR=15.57, 95% CI 2.11 to 114.72, N=228),^{59,68} but not seizures (2.3% vs 0%, RR=5.0, 95% CI 0.24 to 102.6, N=168)⁵⁹ or haemotympanum (2.3% vs 0%, RR=5.0; 95% CI 0.24 to 102.6, N=168) compared to the control groups.^{26,59} The consistency of these effects is unclear, though, as adverse effects were only reported in 3 studies, of 272 patients.^{59,65,68} Reported minor adverse effects include: polypnea (rapid breathing), expiratory dyspnea (difficulty breathing), tinnitus (ringing in the ear), aural fullness (pressure in the ear), disequilibrium, vertigo, and nausea.^{59,65,68}

Because evidence on harms from RCTs of HBOT for TBI and PTSD is likely limited by imprecision, we also considered evidence on harms from other populations. HBOT is generally believed to be safe when used as directed for FDA-cleared indications, none of which include TBI or PTSD.^{3,75} Per the Undersea and Hyperbaric Medical Society, middle ear barotrauma and sinus squeeze are the 2 most common side effects of hyperbaric oxygen in other populations, with an incidence of approximately 2%.⁷⁶ In RCTs of mild TBI, rate of inner ear barotrauma was 8% and 5.91% for “ear barotrauma”.^{25,53,54,63} HBOT 1.5 ATA to 2.4 ATA was associated with a 0.3% rate of seizures based on the most recent and one of the largest retrospective cohorts of 2,334 patients treated for a wide variety of conditions at the Sagol Center of Hyperbaric Medicine and Research in Israel between June 2010 to December 2014.⁷⁷ In 168 patients with moderate to severe TBI, rates of seizures were higher for HBOT 1.5 ATA (2.3%).⁵⁹ Although this may reflect a greater baseline seizure risk in patients with moderate to severe TBI compared to the likely stable outpatient status of the study by Hardanny et al,⁷⁷ this is still higher than critically ill carbon monoxide poisoned patients who were treated with higher pressures of 2.45 ATA (0.3%) or 3.00 ATA (2.0%), but not 2.80 ATA (3.0%).⁷⁸ Therefore, the magnitude of seizure risk in patients with TBI and/or PTSD remains uncertain due to imprecision and inconsistency.

KQ3 & 4: Do the benefits or risks of HBOT differ per patient characteristics (eg, patient demographics, comorbidities, disease severity) or treatment protocol (eg, number of sessions, amount of pressure, inpatient vs outpatient treatment)?

Because of heterogeneity in patient populations and outcome assessment methods, we could not assess if or how benefits and risks of HBOT may differ per patient characteristics or treatment protocol.

SUMMARY AND DISCUSSION

HBOT has the potential to fill a great need by improving the health and well-being of the many patients with TBI and/or PTSD who are refractory to recommended treatments. Interpretation of evidence on using HBOT for TBI/PTSD has been controversial, widely debated, and potentially confusing. Our independent and objective examination of 16 RCTs found that the large treatment benefits demonstrated for HBOT in uncontrolled case series have not been easily replicated in well-controlled RCTs. Potential explanations for this include that the potential benefits are subtle and demonstration requires larger RCTs, HBOT is in fact ineffective, and/or the sham design has indeed been problematic. We are unconvinced that the current evidence clearly points to one explanation over another. We simply still don't know.

For mild TBI, in the most recent fully published VA/DoD-funded RCT (HOPPS), neither HBOT 1.5 ATA nor room air at 1.2 ATA (sham) significantly improved the proportion of military service members with a clinically relevant improvement in post-concussive symptoms after 8 to 10 weeks (≥ 2 -point improvement in Rivermead Post-Concussion Symptoms Questionnaire [RPQ—3]) compared to a no-chamber group (52% vs 33% vs 25%, $P=0.24$). Although the lack of difference between sham and no chamber had the potential to negate the 'mischaracterized sham' argument, the imprecision in HOPPS RCT precluded any conclusions. Compared to sham (10.5% O₂ at 2.0 ATA, room air at 1.2-1.3 ATA) HBOT given at 1.5 ATA to 2.4 ATA for mild TBI also has not significantly improved mean scores on other post-concussive symptom checklists or quality of life outcomes in other fully published VA/DoD RCTs.^{24,25,63} HBOT also did not significantly improve PTSD symptoms compared to sham in 2 VA/DoD studies with concomitant mild TBI and PTSD (mean difference in PTSD score change, -1.49 points (95% CI -5.79 to 2.80)), but interpretation of these findings is limited by imprecision, as only 37% to 65% of study participants had documented PTSD. In patients with moderate to severe TBI, although HBOT may significantly reduce risk of mortality, it is unclear whether the reduction is due to HBOT and not differences in intensity level of medical care and decisions about life-sustaining treatment, or whether functional status and quality of life is meaningfully improved in survivors. Serious harms of HBOT appear limited to use in moderate to severe TBI, in which HBOT increased risk of severe pulmonary complications (13% vs 0%, RR=15.57, 95% CI 2.11 to 114.72, N=228), but not seizures or ear barotrauma. In mild TBI, no serious adverse effects were reported and there were no significant differences between HBOT and control groups in specific adverse events.

Proponents of HBOT for mild TBI and/or PTSD suggest that the main confusion in interpreting the findings of controlled HBOT trials is that the 1.2 to 1.3 ATA control groups have been mischaracterized as sham. Although the Hyperbaric Oxygen Committee of the Undersea and Hyperbaric Medical Society defines HBOT treatment pressure as at least 1.4 times higher than sea level,^{1,24} proponents of the 'mischaracterized sham' argument have suggested that lower pressures are actually active treatments with documented physiological and clinical effects. The evidence of increased blood flow effects of the low-pressure room air conditions that support the 'mischaracterized sham' argument are from samples with chronic toxic encephalopathy, autism, cerebrovascular injury, epilepsy, or migraine and not specific to TBI, and also have the potential to be the result of participation effects.⁷⁹

HBOT proponents have also claimed that VA/DoD RCT investigators (and the medical field in general) are biased against HBOT (and other emerging treatments)^{43,44} and that this bias has led to flaws in the design and interpretation of the VA/DoD RCTs that intentionally or unintentionally underestimate HBOT's effects.⁴¹ In order to be complete, any systematic review needs to investigate and address any concerns about the quality, relevance, and integrity of its included studies. One claim is that a VA/DoD investigator bias against HBOT led to a design that intentionally underestimated HBOT's effects in the Cifu RCT^{24,55,66,67} because it didn't match the HBOT parameters used in the prior Wolf RCT.^{25,53,54} We disagree with the claim that HBOT parameters used in Cifu RCT clearly reflect levels known to be sub- or supra-therapeutic. First, as HBOT parameter best practices for TBI have not yet been identified, some variability among RCTs is inevitable. Second, as the HBOT parameters used in the Wolf RCT did not produce clinically relevant improvement, replication is not clearly warranted. Finally, we interpret the selection of the pressures for the Cifu RCT (2.0 and 1.5 ATA equivalent) as reflecting an attempt to improve the chances of HBOT's effectiveness. This is because the pressure levels used in the Cifu RCT were closer than in the Wolf RCT to the levels that the HBOT proponent also identified as "the ideal pressure that proponents of HBOT normally use for neurological treatments" (≤ 1.5 ATA). We also identified the claim that VA/DoD bias against HBOT led to misinterpretation of the Cifu RCT results: "The conclusion of Cifu et al. that HBOT is ineffective on mTBI is not supported by the data they acquired."⁴¹ To refute the Cifu RCT conclusion and demonstrate HBOT's effectiveness, this claim provides data on within-group, uncontrolled changes from before to after in the HBOT arms from both Cifu and Wolf and from another uncontrolled series of HBOT patients.²⁸ We disagree that these within-group data demonstrate a misinterpretation of results in the Cifu RCT. In fact, in the Cifu RCT publication, the investigators' interpretation of the within-group changes is identical to those of this HBOT proponent, as noted by this quote from the abstract: "Within-group testing of pre- and postintervention means revealed significant differences on several individual items for each group and difference in the Posttraumatic Disorder Checklist—Military Version total score for the 2.0 ATA HBO2 group." The difference is that the conclusion from the Cifu RCT that HBOT is ineffective is based on a between-group's comparison of HBOT versus sham, which we agree was not statistically significant. The problem with relying on within-group changes is that – as even noted by a HBOT proponent – without a control group, placebo or participation effects "cannot be entirely ruled out"²⁸ and "need confirmation with larger numbers of subjects or with a stronger design such as a randomized or Bayesian study."²⁸

Skeptics claim HBOT has consistently shown no significant differences compared to sham and is no more than a high-tech, high-touch ritual³⁶ with "powerful nonspecific placebo effects."³⁷ Factors such as (1) heterogeneity in HBOT protocol (1.5 ATA to 2.4 ATA), outcome assessment methods, timing (immediately following therapy, up to 6 weeks after discontinuation), and patient populations (most recent TBI ranged from 3 to 71 months) and (2) important methodological limitations preclude interpreting these findings as consistent evidence of no effect. We are not suggesting that it is incumbent on the skeptics to prove ineffectiveness. We are only noting the limitations that preclude clear interpretation of the VA/DoD RCTs as demonstrating consistent evidence of no effect.

LIMITATIONS

The evidence base included in this review has several important limitations. First, applicability to Veterans is unclear, as the majority of the RCT participants were active service members who

were temporarily reassigned for study participation, often with greatly reduced duty schedules and enhanced access to leisure time and activities – sometimes in a noncombat, semitropical beach environment. Second, for considering use of HBOT for patients in whom other treatments have been unsuccessful, evidence is insufficient to support recommendations about specifically when to initiate HBOT in the order of recommended conventional pharmacotherapies and psychotherapies. How much failed conventional therapy is “enough” before trying HBOT? Although it is likely that many study participants had already failed “gold standard” therapy, available studies’ lack of specific criteria for establishing “failure” of conventional therapy, and/or dose and duration and order of conventional therapies, limits applicability to specific patients. Third, heterogeneity in patient populations and outcome assessment methods prevented assessment of whether and how benefits and risks of HBOT may differ per patient characteristics or treatment protocol. Finally, the most significant limitation of the current literature base is a lack of assessment of clinically relevant outcomes and durability of HBOT beyond immediately after or in the few weeks after HBOT completion. Among the 5 RCTs of HBOT for TBI, PTSD and/or PPCS currently in progress – 4 in the US and 1 in China – none appear to sufficiently address these gaps in the existing evidence (See Appendix F for a complete table of Research in Progress).

In terms of our review methods, limitations include our literature search with exclusion of non-English studies and our scope. Although we focused on the most clinically relevant outcomes of mortality, morbidity, quality of life, functional capacity, and clinically significant symptom response, we recognize this may limit the applicability of our findings to a broader range of intermediate outcomes, including physiological measures, patient expectations, and mean changes in symptom scale scores.

CLINICAL AND FUTURE RESEARCH IMPLICATIONS

Due to the lack of compelling evidence of effectiveness, guidelines and policies discouraging broad coverage of HBOT for mild TBI appear reasonable. Due to the lack of consistent evidence of ineffectiveness and no clear red flags for serious harms, we agree with the option suggested by proponent Paul Harch, MD of further evidence development on HBOT for TBI and/or PTSD of “an economical Civilian/DoD/Veterans Affairs (VA) off-label networked hyperbaric treatment program using a Medicare-like Coverage with Evidence Development pathway”⁷⁹ for Veterans in whom other treatments have not been successful. Because reasons for lack of expected improvement can be complex and multidimensional, including failure to receive evidence-based interventions due to variability in clinician judgment and patients’ barriers to access and adherence, to avoid potential further delay of evidence-based treatments, we suggest careful documentation of previous treatments prior to HBOT initiation. To best contribute to further HBOT evidence development, ideally TBI and/or PTSD, comorbidities, and baseline severity and duration of symptoms should be well-documented, and assessment of effects on clinically important benefits as recommended by the VA/DoD CPG, including functioning, well-being, and quality of life, should be prioritized. Although likely not possible for a small clinical demonstration, clinical evaluation should be done in tandem with neuroimaging and assessment of the role of potentially exaggerated patient expectations that may have resulted due to publicized reports of HBOT as a “miracle cure”. As any positive effects of HBOT should not come at the expense of increased risk of serious harm, assessment of the adverse effects of HBOT is also important. To best consider the use of add-on HBOT for Veterans with TBI and/or PTSD in whom other treatments have been unsuccessful, documentation of the types and

durations of previous and ongoing treatments would also be informative in assessing the generalizability of available evidence. Additionally, as the most recent VA/DoD RCTs (HOPPS and BIMA) used identical comparison groups of HBOT 1.5 ATA and room air 1.3 ATA and assessment tools and had similar military populations, to increase statistical power we suggest further analysis of their pooled data. Although likely cost-prohibitive, if another RCT is undertaken, we recommend replication of the HOPPS study design with a wait-list usual care no-chamber group, a low-pressure group, and a 1.5 ATA group, but with an adequate sample size to detect a difference on clinically important outcome, done in tandem with neuroimaging and assessment of the role of patient expectations to help add meaning to why any improvements may be occurring and potentially shed light on the sham debate. To improve our knowledge about HBOT's potential to improve clinically meaningful outcomes, we suggest establishment of a set of validated outcome measures including minimally important symptom difference thresholds. To control for potential natural waxing and waning of symptoms and evaluate durability, we suggest outcome assessment at multiple time points during and 6 to 12 months post-treatment. To potentially improve consistency in interpretation of future HBOT RCT results, we suggest that future HBOT investigators consult with and document endorsement from HBOT proponents on RCT design.

CONCLUSIONS

Current evidence does not clearly point to one explanation over another for why well-controlled RCTs have not easily replicated the large treatment benefits demonstrated for HBOT in uncontrolled case series. Although our independent and objective examination of 16 RCTs found a lack of compelling evidence of effectiveness for mild TBI and PTSD, we disagree that it can be fully explained by potential physiological effects of sham specific to TBI and/or PTSD or consistent evidence of ineffectiveness that points to a nonspecific participation effect. Pooling data from the HOPPS trial and the as-yet-unpublished BIMA trials could shed light on the debate. Broad usage of HBOT as an initial treatment for mild or moderate to severe TBI or PTSD in lieu of conventional treatments still does not appear clearly warranted. When patients do not respond to and/or do not tolerate adequate trials of multiple conventional therapy options and are considering emerging treatment options, offering HBOT to Veterans with mild or moderate to severe TBI and/or PTSD appears reasonable – with careful consideration of potential increased risk of certain harms. A small-scale clinical demonstration may provide the opportunity to improve data collection on comorbidities, clinically relevant patient outcomes, patient expectations, and documentation of the types and durations of previous and ongoing treatments.

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