SUMMARY OF Studies on HBOT for TBI/PTSD

Four pivotal US-based clinical trials and one Israeli-based clinical trial have provided well-structured and controlled studies that demonstrate reparative effects in mTBI/PPCS symptoms with HBOT. Improvements in TBI and post traumatic stress disorder (PTSD) symptom scores for the 2 DoD/VA-sponsored studies, the Army-sponsored study of Miller et al., a civilian-sponsored study of Harch et al., and the Israeli civilian study of Boussi-Gross et al. have demonstrated both clinical and statistically significant improvements from baseline measures after undergoing 30–40 1-hour HBOT treatments during the course of the trials. All participants had documented TBIs and were at least 2 years into the PPCS phase of the injury, ensuring that spontaneous recovery was a highly unlikely factor." Xavier A. Figueroa, PhD and James K. Wright, MD (Col Ret), **USAF *Hyperbaric Oxygen: B-Level Evidence in Mild Traumatic Brain Injury Clinical Trials.*** Neurology® 2016;87:1–7

The authors summarize their analysis: "**There is sufficient evidence for the safety and preliminary efficacy data from clinical studies to support the use of HBOT in mild traumatic brain injury/ persistent post concussive syndrome (mTBI/PPCS). The reported positive outcomes and the durability of those outcomes has been demonstrated at 6 months post HBOT treatment. Given the current policy by Tricare and the VA to allow physicians to prescribe drugs or therapies in an off-label manner for mTBI/PPCS management and reimburse for the treatment, it is past time that HBOT be given the same opportunity. This is now an issue of policy modification and reimbursement, not an issue of scientific proof or preliminary clinical efficacy."** http://bit.ly/2xEZSz9

**Wolf-Cifu Study

https://treatnow.org/knowledgebase/wolf-studyj-neurotrauma-2012-3/

Conclusion: Hyperbaric oxygen is a potent intervention for acute ischemic injuries that has a sound theoretical underpinning and demonstrated efficacy in dive-related injuries, soft tissue healing, and carbon monoxide poisoning. Human research trials with acute severe TBI have been inconclusive. The current study in participants with postconcussive syndrome from chronic mTBI demonstrates no efficacy in symptom relief with HBO2 at an exposure pressure of 2.4 ATA for 90 min given once daily for 30 treatment series, is expensive, exposes patients to potential side effects, and has limited availability, clinical usage is not warranted for the management of symptoms of chronic mTBI at this treatment pressure. It is recommended that larger, multicenter, randomized, controlled (both sham-control and wait-list), double-blinded clinical trials be conducted at lower total oxygen doses as recommended by AHRQ.

What their own discussion says: "While it is possible the sham-control condition had a ''therapeutic'' effect on brain recovery, relative to the oxygen partial pressures attained during clinical hyperbaric treatments at 2.0–3.0 ATA, it seems very unlikely such a minimal dose of oxygen and nitrogen could influence brain function favorably." [Research demonstrates that ANY increase in pressure and/or oxygen has medicinal effects. Thus, their "seems very unlikely" comment is without merit since they didn't test it, while others have for over a decade. The May 2022 redefinition of hyperbaric medicine by the UHMS further cements the proof in the data.] And: "PCL-M composite scores and ImPACT total scores for sham-control and HBO2 groups revealed **significant improvement over the course of the**

study for both the sham-control group (t = 3.76, p = 0.001) and the HBO2 group (t = 3.90, p = 0.001)." [I.e., everyone showed "significant improvement" over the non-HBOT groups."]

**Cifu-Hart Study

https://treatnow.org/knowledgebase/cifu-the_effect_of_hyperbaric_oxygen_on_persistent-99821-1/

Conclusion: This study demonstrated that HBO2 at either 1.5 or 2.0 ATA equivalent had no effect on postconcussion symptoms after mild traumatic brain injury when compared with sham compression.

What their own discussion says: "there were within-group improvements on several of the items for each of the 3 compression groups" and "within-group analyses were noteworthy for improvements on 1 to 2 items from both the RPQ and the PCL-M within each experimental condition. In addition, the total score for the 2.0 ATA equivalent group for the PCL-M was found to improve." And "our study demonstrated a significant reduction in some individual items on both the RPQ and the PCL-M that are commonly attributed to stress in both the sham control group and the HBO2 group over time."

**JAMA Miller HOPPS Study

https://treatnow.org/wp-content/uploads/2015/10/JAMA-Miller-Study-and-Commentary-2.pdf

Conclusion: "Both intervention groups demonstrated improved outcomes compared with PCS care alone. This finding suggests that the observed improvements were not oxygen mediated but may reflect nonspecific improvements related to placebo effects. [Here we see the introduction of the "placebo effect" as the conditional explanation for improvements in all patients.]

What their own discussion says: "The group randomized to no supplemental chamber intervention showed no improvement……. The group receiving HBO improved symptomatically…….The group receiving sham sessions also improved….. The PTSD symptoms improved after the interventions [with HBO]….. the Global Satisfaction With Life Scale demonstrated similar improvement with both chamber interventions compared with routine PCS care…… ***our results support the conclusion that supplemental administration of breathing 100% oxygen at 1.5 ATA (HBO procedure) or air at 1.2 ATA (Sham procedure) for 60 minutes is well tolerated and improves symptoms and quality of life compared with local care management of PCS with out chamber intervention……. Among service members with PCS, HBO showed no benefits over air sham compression procedure, but symptoms in both groups improved compared with mTBI care without supplemental chamber interventions."***

A COMMENTARY included in the JAMA publication says: "no new treatments for persistent blast or impact-related postconcussion symptoms have been identified, despite the extensive investment to date [Note: ~$186M] The evidence remains weak and inconsistent for both pharmacological (e.g., stimulant or cholinergic augmentation) and nonpharmacological (eg, cognitive rehabilitation) interventions……. These findings reinforce the argument that effective interventions do not yet exist within the present structure of care or that routine post-concussion interventions within the DoD or

VHA may even have iatrogenic effects [e.g., an iatrogenic illness is an illness that is caused by a medication or physician. i.e., current interventions are making patients worse.]……..[HBO] was a healing environment ……. ***HYPERBARIC OXYGEN TREATMENT DOES NOT WORK, BUT THE RITUAL OF INTERVENTION DOES."*** **[**This so-called "Ritual of Hyperbarics" is an interesting circumlocution. It is as void of science as was the original definition of Hyperbaric Medicine that the UHMS has now corrected to comply with the laws of physics, physiology, and biochemistry.]

**Weaver BIMA Study

https://www.uhms.org/images/chapters/Pacific/2018/Weaver_BIMA_HBO2_RCT_mTBI_DoD_UHM_45-2_2018.pdf

Conclusion: "By 13 weeks, HBO2 improved post-concussive and PTSD symptoms, cognitive processing speed, sleep quality, and balance function, most dramatically in those with PTSD. Changes did not persist beyond six months."

What their own discussion says: "In BIMA, participants receiving HBO2 had improved post-concussive and PTSD symptoms, sleep quality, and some anger and memory outcomes compared to sham at 13 weeks. Improvements with HBO2 were sometimes larger in participants with PTSD. The magnitude of improvement was clinically meaningful but did not restore BIMA participants to normal"……" In all four military-sponsored studies, participants exposed to HBO2 reported symptom improvement. In two trials, participants exposed to sham also improved. ***The magnitude of improvement in self-reported assessments by 13 weeks is larger than any non-hyperbaric intervention previously reported***."

**Wolf et al [USAF] Reassessment of data in Study #1

https://treatnow.org/knowledgebase/usaf-reappraisal-of-wolf-cifu-study-2015-2/

Conclusion: "both groups showed improvement."

What their own discussion says: "Of note, PCL-M composite scores and ImPACT total symptoms scores for both sham-control and HBO2 groups revealed improvement over the course of the study……. Both groups clinically improved……. Jaeschke, Singer and Guyatt [41] first proposed that research results be looked at from not only a distributive perspective but also from the patient's perspective. This they termed the minimal clinically important difference (MCID) as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in absence of troublesome side effects and excessive cost, a change in the patient's management." Since 1989, this has evolved into anchor-based estimates. The choice of anchor is application-specific to the clinical measure and seemingly becomes more refined as research on the clinical measure matures. However, the focus of clinical trial results can also focus on establishing the MCID more so than the minimally detectable change defined by statistical significance [42]. The statistical estimate (which is independent of the psychological MCID) is a change of a 0.5 standard deviation. In this study, the MCID is best seen in the PCL-M data. The reliable change and statistically significant change are addressed in the National

Center for PTSD PCL handbook [43], and their pedigree can be traced back to these concepts. In 1984, Jacobson and Follette [44] defined clinically significant change as "the extent to which therapy moves someone outside the range of the dysfunctional population or within the range of the functional population." In other words, viewing patients entering therapy as part of a dysfunctional population and when departing from therapy as no longer belonging to that population would be considered having significant change. Their rationale is best described in Jacobson's comments: "First, the tests provide no information on the variability of response to treatment within the sample; yet information regarding within-treatment variability of outcome is of the utmost importance to clinicians. Second, whether a treatment effect exists in the statistical sense has little to do with the clinical significance of the effect. The existence of a treatment effect has no bearing on its size, importance, or clinical significance. Questions regarding the efficacy of psychotherapy refer to the benefits derived from it, its potency, its impact on clients, or its ability to make a difference in peoples' lives. Conventional statistical comparisons between groups tell us very little about the efficacy of psychotherapy" [45]…… Wolf showed neither the PCL-M scores nor the symptoms inventory from ImPACT were significantly different between the sham (1.3 atm abs) and 2.4 atm abs exposure groups, yet both groups had an improvement trend (11). Hyperbaric oxygen also appeared safe, with side effects in TBI subjects at 2.4 atm abs being no different than in the 1.3-atm abs subjects [10]…….. This pilot study demonstrated no obvious harm, including seizure, observed at the higher dose of 2.4 atm abs for 90 minutes…….. Jaeschke's definition and philosophy regarding his MCID are remarkably similar to the AHRQ 2003 report evaluating the use of hyperbaric oxygen for TBI. The recommendations section stated: "If there is a 1 percent chance that the treatment works, a rational decision maker would try it – there is a potential gain and no potential loss. On the other hand, if there are proven harms, and their severity and frequency are well described, the probability that the treatment works would have to be higher before most people would try it" [9]. Our previous publication from the study demonstrated hyperbaric exposures as high as 2.4 atm abs were safe and comparable in side effects to the sham in the TBI population. This is important in that this pressure is used as a standard treatment for patients worldwide on a daily basis, many of whom may have had TBI. Subgroup analysis of cognitive changes and PCL-M results regarding PTSD demonstrated a relative risk of improvement using 2.4 atm abs hyperbaric oxygen. There is a potential gain and no potential loss. The VA/Clinical Practice Guidelines define a "B evidence rating" as "a recommendation that clinicians provide (the service) to eligible patients. ***At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm"*** [2].

All 20 studies are available in the attached Excel spread sheet. This SHAM DISCUSSION Paper compiles professional commentary on the now-disproved "sham" utilized by USG studies.

Hyperbaric Oxygen and SHAM Discussion and Challenges

Two definitions of "sham" interest us in this discussion:

1. ***sham (n): something that is not what it purports to be; a spurious imitation; fraud or hoax***.

In the case of DOD/VA/Army medicine, arguments and conclusions by the government about the use of HBOT for TBI/PTSD/Concussion are a sham: a scientific error that was rectified in May 2022 by the UHMS. Their research ***DATA*** and ***DISCUSSION***, however, state categorically that HBOT is safe and effective:

Summary of positive findings in Army Studies: Army medicine has run trials investigating the use of Hyperbaric Oxygen to treat and help heal Traumatic Brain Injury. They have shown that HBOT is both safe and effective: "***Randomization to the chamber . . . . offered statistical and in some measures clinically significant improvement over local routine TBI care.***" Also: ".... ***total scores for [both] groups revealed significant improvement over the course of the study for both the sham-control group .... and the HBO2 group***....." Expert outside consultants to DOD declared that ***"[HBOT] is a healing environment."*** Ten years, over a hundred patients, and over $180M later, five studies discuss the mystery of everyone getting better and keep searching for the secret of the placebo.

A 2015 USAF paper reanalyzing the data in the cornerstone DOD/VA/Army study concludes: "This pilot study demonstrated no obvious harm [and] both groups showed improvement in scores and thus a benefit. Subgroup analysis of cognitive changes and PCL-M results regarding PTSD demonstrated a relative risk of improvement . . . . ***At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm***. . . [emphasis added] Hyperbaric oxygen therapy for mild traumatic brain injury and PTSD should be considered a legitimate adjunct therapy. . . ."
http://bit.ly/2faBldN

2. **"sham" as part of a clinical trial.** In a sham treatment, the researcher goes through the motions without actually performing the treatment. The intent is to have an ***inert or medically inactive procedure or substance*** used to compare results with active substances.

A placebo is often used in a drug trial to help show whether the drug being studied is more effective than an inactive "sugar pill." Some of the people in the drug trial get the active drug while others get the inactive placebo. The results of each group are compared. [NOTE: current Randomized Controlled Trials were designed for drugs. Oxygen is a drug, and HBOT has been declared both a drug and a device. As such, it is extremely difficult to construct a sham for HBOT given both the natures of oxygen and pressure, and the physical effects experienced by a subject during pressurization and depressurization.]

In a sham treatment, some people get the real treatment while others get the sham treatment. Then the results are compared.

When a person who is taking the inactive substance or who has had a true sham treatment reports that symptoms have improved, this improvement is called the placebo effect. It is probably a result of the brain releasing "feel-good" hormones such as endorphins in response to treatment. Active drugs and therapies can also have a placebo effect. It can be difficult in some cases for researchers or doctors to know if the reason a drug works is because of its active ingredient or because of the placebo effect.

Challenges to DOD/VA/Army claims of "sham" and findings that HBOT does not work for TBI.

1. "We have much more knowledge about the physiology of hyperbaric therapy in neurological conditions (ref) and this should help us understand and accept the impact of small increases of pressure on brain function. By definition “sham” is “something false or empty”. Hyperbaric treatments at 1.2 ATA substantially increase the amount of dissolved oxygen in the blood and simultaneously induce cascades of metabolic changes and genes activation. Therefore, the supposedly sham treatment of Miller’s study is not close to being a placebo. An increase of just 0.2 ATA is an effective treatment and is used to save lives in patients with mountain sickness. It has to be considered as a treatment arm. Always. . . . True science should always be guided by facts and rigor, not by beliefs. Scientific knowledge and paradigms are in constant evolution. If there were no preconceived idea on the amount of pressure needed to induce a positive response on postconcussion patients, the only scientific conclusion we could draw from the significant results described in Miller’s controlled study is that, even at small pressures HBOT seems to be effective. This could have a significant impact on the quality of life of thousands of military personnel. " ***Pierre Marois MD, FRCP(c), Physiatrist, Dept. of Pediatrics and Dept. of Rehabilitation, Ste-Justine University Hospital, Montreal, Canada, Letter to the Editor, JAMA, 10/20/2016.***

2. In a retrospective safety study of a single site that treated 8,100 patients in a 22 year period, non-fatal incidents occurred in less than 1% of patients, with zero fatalities. A 73 year review of hyperbaric medicine world-wide, revealed that fatal accidents or explosions have not occurred in North America up to 2008, making it one of the safest clinical procedures in medicine. HBOT and HBAT are important tools to help repair damage to the brain and should be a standard treatment in support of a functional medicine approach to recovery and health maintenance. Veterans and active duty members are killing themselves due to TBI and PTSD. HBOT can provide a much-needed intervention to improve symptoms and begin healing the brain. HBOT is not a silver bullet, but when managed in an integrative and functional medicine approach (diet, hormone rebalancing, heavy metal chelation, meditation, therapy) you will restore a broken brain and body into a functional brain and body. . . . All three study groups [DOD/VA/Army] (Wolf et al., Cifu et al. and Miller et al.) . . . . suffered from weaknesses in design of the trials: The “sham” interventions used in the three trials (DoD/VA, Army) were not shams, but different doses of an active ingredient (or ingredients). The design flaw in each study invalidates the conclusions of a placebo effect, supporting the alternate conclusion: HBOT and HBAT are both neuroprotective and neurorestorative. The controls that the study authors used were defined as shams, but all the evidence points to pressurized air (21% O2) having biological and therapeutic activity. ***The 900 lb Gorilla in Hyperbaric Medicine.*** By Xavier A. Figueroa, Ph.D. ***http://bit.ly/2yFZEF8***

3. "There is sufficient evidence for the safety and preliminary efficacy data from clinical studies to support the use of HBOT in mild traumatic brain injury/ persistent post concussive syndrome (mTBI/PPCS). The reported positive outcomes and the durability of those outcomes has been demonstrated at 6 months post HBOT treatment. Given the current policy by Tricare and the VA to allow physicians to prescribe drugs or therapies in an off-label manner for mTBI/PPCS management and reimburse for the treatment, it is past time that HBOT be given the same opportunity. This is now an issue of policy modification and reimbursement, not an issue of scientific proof or preliminary clinical efficacy." Xavier A. Figueroa, PhD and James K. Wright, MD (Col Ret), **USAF *Hyperbaric Oxygen: B-Level Evidence in Mild Traumatic Brain Injury Clinical Trials.*** Neurology® 2016;87:1–7 ***https://bit.ly/2zoIzBv***

4. A study of the effect of hyperbaric oxygen treatment of severe brain injured patients has been published already two decades ago. Several prospective clinical trials on treatment of mTBI have been published in the last decade [31,32,33], and three studies published in the last two years addressed the effect of HBOT on chronic mild TBI patients. However, the reported beneficial effects of the hyperbaric treatment were severely questioned by the medical community and triggered high skepticisms to the extent that TBI and stroke patients in the US are rarely treated by hyperbaric oxygen. The HBOT option has been dismissed by the medical community on the grounds of: 1. Lack of knowledge about the connection between metabolism and neuroplasticity. 2. Lack of randomized clinical trial with standard placebo control. 3. Sham control with room air at 1.3Atm yielded significant improvements. These issues are clarified and elaborated on in the discussion section. The placebo dilemma People can sense a pressure increase beyond 1.3Atm, hence standard placebo, with normal air pressure, for HBOT could perhaps be attained by exposing the patients to normal pressure combined with falsifying stimulation (e.g., by increasing and decreasing the pressure), which generates a fictitious pressure sensation. Since breathing normal air under hyperbaric conditions leads to elevated tissue oxygen (e.g., about 50% for 1.3Atm), standard placebo could also be attained by giving the patients compressed air with sub-normal oxygen concentration. In the discussion section we explain that the first approach can be effective only for some patients and poses logistic difficulties and the second approach involves ethical issues. In an attempt to evade the placebo dilemma, a recent study of HBOT for mTBI compared the effect of 100% oxygen at 2.4Atm with the effect of room air at 1.3Atm as sham control. The study found significant improvements in both groups and with slightly higher efficacy at 1.3Atm. Based on these results, the authors presented a sweeping conclusion that their study shows that HBOT has no effect on post mTBI brain damage and the observed improvements resulted from placebo associated with spending time in the hyperbaric chamber. As is discussed in great details in the discussion section, we reason that the authors reached wrong conclusions for two main reasons. First, room air at 1.3Atm cannot serve as a proper sham-control since it is not an ‘‘ineffectual treatment’’ (as is required from placebo) since it leads to a significant increase in the level of tissue oxygenation which has been shown to be effective. Second, 100% oxygen at 2.4Atm leads to too high oxygen levels which can cause inhibitory effect or even focal toxicity. ***Hyperbaric oxygen can induce neuroplasticity and improve cognitive functions of patients suffering from anoxic brain damage. Restorative Neurology and Neuroscience 33 (2015) 471–486*** ***https://bit.ly/2ZwDj9l***

5. "[DOD/VA/Army studies are] mischaracterized as a sham-controlled study based on an incomplete non-physiologic definition of hyperbaric therapy. Walker, et al1 intended and claimed to have measured within-group treatment effects of different doses of hyperbaric therapy and between-group differences in treatment effects of HBOT vs. sham air treatments, but did not measure any within-group treatment effects and did not compare any between-group treatment effects, according to their statistical analysis. In addition, they could not compare HBOT to sham due to the absence of a true non-treatment control group, the absence of any within-group treatment effects on any outcome instrument, and the omission of the proper statistical analysis. As a result, it appears that both the study and conclusions are misleading and invalid. Walker, et al1 is a dose-finding study of three composite doses of pressure or pressure and hyperoxia which have not been tested before on mTBI PPCS and whose treatment effects in SMs with mTBI PPCS are unknown. It is a shame that hundreds of thousands of brain-injured U.S. SMs,[21] millions of Americans, and dozens of millions of patients worldwide are dependent on the veracity of this study and its companion DoD studies for decision-making on a potentially salutary therapy. " ***Hyperbaric Oxygen for Postconcussion Syndrome: Persistent Mischaracterization of DoD Studies, Inappropriate Statistical Analysis, Invalid Conclusions***. By Paul G. Harch, M.D. ***https://bit.ly/2LrcbUv***

6. Compressed air has physiological actions and is neither sham nor placebo. Using controlled conditions, Scott Miller et al have added yet more evidence that hyperbaric treatment is of benefit to patients with mild neurological conditions. This was clearly not the intention of this pilot study but the attribution of the remarkable improvements recorded to 'ritual' demonstrates that the science involved is not understood. A 20% increase in ambient air pressure cannot be regarded as a "sham" treatment because the concentration of the respired oxygen increases from 158 to 190 mm Hg (at a barometric pressure of 760 mm Hg). As the alveolar water vapour and carbon dioxide partial pressures remain constant there is a proportionally greater increase in the plasma oxygen tension and an abrupt increase in respired gas concentrations is also accompanied by beneficial osmotic changes at cellular level. The dramatic effect of a higher oxygen concentration is evident in fossil records: when the Earth's atmosphere was about 35% the wingspan of dragonflies reached 30 inches. Neglected is the recent research showing that cellular oxygen concentrations regulate the expression of our most important genes, including vascular endothelial growth factor and those controlling inflammation. Recent studies of using compressed-air as a treatment for brain damaged infants have shown the same remarkable improvement, but the most dramatic confirmation of the importance of a modest increase of air pressure comes from experience at high altitude. All high altitude climbers know that both pulmonary and neurological symptoms are improved, indeed usually resolved, by the increase in air pressure produced by a descent. During WW2 a pressure bag was used to great effect in treating altitude sickness in experiments conducted in a B24 Liberator - the forerunner of the portable hyperbaric chambers now used by high altitude climbers and the US Army Special Operations Command. As a small increase in air pressure can resolve a mountaineer's life-threatening pulmonary and cerebral oedema, the subtle residual problems that follow concussion will surely benefit from hyperbaric air treatment. The pressure needed can easily be achieved by pressurizing a commercial aircraft on the ground: a Boeing 747 would allow hundreds of service men to be treated at a time at minimal cost. . . . Few

medical professionals outside of aviation, space and underwater medicine understand the importance of barometric pressure. The use of hyperbaric oxygen treatment must be included in the curricula of our medical schools: we have no substitute for the gas***. Philip B James MB ChB DIH PhD FFOM, Emeritus Professor of Medicine University of Dundee Scotland***

7. “To our knowledge, these findings support the likelihood of biologic activity, consubstantial with HBOT, being activated at much lower dose of hyperoxia than previously postulated [~1.2ata]. Future research examining oxygen/dose relationship will further elucidate the biological effect of various doses of hyperoxia, and establish differences between concentration and pressure, along with establishing basal active levels. MacLaughlin KJ, Barton GP, Braun RK, MacLaughlin JE, Lamers JJ, Marcou MD and Eldridge MW (2023**) Hyperbaric air mobilizes stem cells in humans; a new perspective on the hormetic dose curve.** Front. Neurol. 14:1192793. doi: 10.3389/fneur.2023.1192793