



## **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 has been exposed over and over, year after year. 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.**"

This recent 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. . . .

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 a 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 changes experienced by a subject during pressurization and depressurization.]

In a Randomized Controlled Trial where a sham is invoked, 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 experienced a real 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 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. In a retrospective safety study of a single site that treated 8, 100 patients [30] 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 [31] 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. ***The 900 lb Gorilla in Hyperbaric Medicine.*** By Xavier A. Figueroa, Ph.D.

2. "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

3. 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 resented 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***

4. "All three study groups [DOD/VA/Army] (Wolf et al., Cifu et al. and Miller et al.) . . . suffered from a 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% O<sub>2</sub>) having biological and therapeutic activity. ***The 900 lb Gorilla in Hyperbaric Medicine.*** By Xavier A. Figueroa, Ph.D.

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.

6. "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), Psychiatrist, Dept. of Pediatrics and Dept. of Rehabilitation, Ste-Justine University Hospital, Montreal, Canada, Letter to the Editor, JAMA, 10/20/2016.***

7. Compressed air has physiological actions and is neither sham nor placebo. Using controlled conditions, Scott Miller et al1 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.<sup>2</sup> 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,<sup>4,5</sup> 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 pressurising 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.

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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***



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