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Chapter

Hyperbaric Oxygenation in the Treatment of Traumatic Brain Injury

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Abstract

Hyperbaric Oxygen Therapy can help heal brain wounds: TBI/PTSD/Concussion. Peer-reviewed positive scientific and clinical evidence in over 7500 cases demonstrates that HBOT helps heal wounded brains and returns patients to a life denied them by DOD/VA/Army that will not talk about, or even use or pay for HBOT treatment for TBI/PTSD/PCS/Concussion. Successful treatment with HBOT [40 one-hour sessions] virtually eliminates suicidal ideation, an effective "suicide prevention" method. Patients also reduce their drug intake to nearly zero and experience 50% reduction in pain and time to withdrawal. The history of HBOT for TBI is littered with bad science, but evidence-based and clinical medicine data show the safety, efficacy and cost effectiveness of HBOT as a standard of care that should be put on-label and insured.

Keywords: hyperbaric oxygen, TBI, PTSD, concussion

> *"The truth goes through three stages: first, it is ridiculed, then it is violently opposed, and then, it is accepted as self-evident."*
>
> **Arthur Schopenhauer**

> *"First they ignore you, then they laugh at you, then they fight you, then you win."*
>
> **Mahatma Gandhi**

1. Introduction

Though neither of these quotes is quite true, they lead this introduction because those who are working to heal broken brains and stop the suicide epidemic are closer to winning than when they started. There are no guarantees that collective successes will overcome medical resistance to accepting the obvious: what "they" are doing does not work to heal brain wounds, and "they" ignore and denigrate a safe and effective treatment that does. Yet those trying to get urgent help to suicidal brain wounded service members see victory on the near horizon for the varieties of truths told in the research and worldwide clinical medicine. As with many advances, an anecdote helps elucidate the main point: changing minds and medicine, even with science, data and facts, is not easy work.

Two renegade Australian MDs, Barry Marshall and J. Robin Warren, in **1981** knew there was a simple treatment for gastritis and peptic ulcers: an antibiotic to kill Heliobacter pylori bacteria. Now, Helicobacter pylori may be the most successful pathogen in human history. While not as deadly as the bacteria that cause tuberculosis,

cholera, and the plague, it infects more people than all the others combined. Yet conventional medicine already knew that ulcers were caused by stress. An entire set of industries grew up around "healing" stress and its aftermath: antacids, stomach surgery for bleeding ulcers, gastritis, stomach cancer, depression. "To gastroenterologists, the concept of a germ causing ulcers was like saying that the Earth is flat." [1] To them, the cause of all the illness and death was psychosomatic, "all in the head." Marshall went so far to prove his point that he gave himself ulcers by drinking a broth of H.pylori and curing himself. And still not recognition. Cut to the chase: For their relentless persistence and science on H.pylori, in **2005** Marshall and Warren won the Nobel Prize. Treatment with an antibiotic is standard medicine for stomach cancer [2]. Twenty-four years to go from goats to Nobel laureates. Along the way, the men were ridiculed and denounced by learned councils around the world. And then the "truth."

As you read these pages, we expect that you will be whipsawed by the truths exposed as authors and readers wonder about the answer to the Obvious Question: *Since this works, why are they opposed to it?* As you will see, there are no complete answers, but the data and the peer-reviewed research do provide compelling and overwhelming evidence of the safety, efficacy, and cost-effectiveness of this treatment. Over 7500 successes cannot be entirely wrong.

2. Background

On August 30, 2002, Medicare announced its intention to issue a national coverage determination (NCD) for Hyperbaric Oxygen Therapy (HBOT) in the treatment of diabetic wounds of the lower extremities. The arguments that led to that determination [3] established that oxygen under pressure was safe and effective for this fourteenth indication, or disease state.

The evolution in thinking and the subsequent research was enabled by the 1999 refinement and restatement of the drug definition of HBOT as the use of greater than atmospheric pressure oxygen as a drug to treat basic pathophysiologic processes and their diseases [4]. The UHMS defines hyperbaric oxygen (HBO2) as an intervention in which an individual breathes near 100% oxygen intermittently while inside a hyperbaric chamber that is pressurized to greater than sea level pressure (1 atmosphere absolute, or ATA) [5]. With that definition the totality of on-label indications could be understood as cohesive sets of diagnoses connected by HBOT effects on the acute and/or chronic underlying pathophysiology common to the diseases.

Doctors noticed that the definition necessarily could be applied to the use of HBOT for additional diseases that shared this pathology. Of the 14/15 indications accepted by the FDA/CMS, at least five are non-healing wounds and therefore closely related to brain wounding from blast, falls, impact, stroke, Improvised explosive devices, and concussion. Those indications are: Crush injury, compartment syndrome, and other acute traumatic ischemias; Arterial Insufficiency, entailing enhancement of healing in selected problem wounds (includes uses like Diabetic Foot Wounds, Hypoxic Wounds); Radiation tissue damage (soft tissue and bony necrosis); Skin grafts and flaps (compromised); and Air or gas embolism (resulting from rapid decompression and blast injury [6].)

The accurate drug definition of HBOT, and its implications for the findings and data in research into traumatic brain injury, is used in this paper to argue for HBOT safety and effectiveness in the treatment of Traumatic Brain Injury. The argument is constructed by identifying the underlying pathophysiology in traumatic brain injury. Evidence for the beneficial effects of HBOT on TBI is presented. Benefits to patients with TBI is discussed. Evidence for HBOT for TBI risk/benefit and cost/are discussed. The conclusion is simple: coverage of HBOT for TBI.

3. Traumatic brain injury basics

Research over the last two decades has revealed the complex microcosms of multiple pathophysiological processes resulting from insults to the brain, including traumatic brain injury [7]. The three essential components determining the outcome of head injuries are brain blood flow; the pressure in the skull leading to swelling; and hypoxia, the lack of oxygen [8].

According to the Centers for Disease Control and Prevention (CDC), "traumatic brain injury (TBI) is caused by a bump, blow or jolt to the head or a penetrating head injury that disrupts the normal function of the brain." TBI severity ranges from "mild," i.e., a brief change in mental status or consciousness to "severe," i.e., an extended period of unconsciousness or amnesia after the injury [9]. The CDC keeps current statistics on TBI death and disability.

Traumatic brain injury (TBI) is a major cause of death and disability in the United States. Those who survive a TBI can face effects that last a few days, or the rest of their lives. Among TBI-related ED visits and hospitalizations in 2014, statistics notable for the CDC include:

- Hospitalization rates were highest among persons 75 years of age and older
- The highest rates of ED visits included persons 75 years of age and older
- For adults 55 years of age and older, falls were the leading cause of hospitalizations and ED visits
- Among TBI-related deaths in 2014, rates were highest for persons 75 years of age and older
- In 2014, an average of 155 people in the United States died each day from injuries that include a TBI
- Between 2001 and 2010, the estimated average annual numbers of TBI in the US equaled: TBI contributed to the deaths of 56,800 people; 282,000 hospitalizations; and 2.5 M ER visits.
- Accidental traumatic brain injuries contributed to more deaths than suicides and homicides together [10].
- Approximately 5.3 M people in the US live with a permanent TBI [11]
- The lifetime economic cost of TBI, including direct and indirect medical costs, was estimated to be approximately $76.5 billion (in 2010 dollars) [12].
- Current estimates put the yearly costs of TBI among veterans at $48 billion [13].

UCLA researchers, citing animal and human studies, speak of "a neurometabolic cascade of events that involves bioenergetic challenges, cytoskeletal and axonal alterations, impairments in neurotransmission and vulnerability to delayed cell death and chronic dysfunction.. .. linking the neurometabolic cascade to clinical characteristics as well as on new connections being made between acute post-concussion pathophysiology, long-term biological changes and chronic sequelae." [14] Further: "The etiology of postconcussive syndrome is debated, but may be caused by diffuse axonal injury or persistent metabolic alterations resulting in neuronal dysfunction and develops in 38–80% of patients with TBI...." [15].

Advanced neuroimaging reveals the basic neurobiology of concussion/mild TBI in animal models, which is increasingly corroborated in human studies. These images of the brain with such techniques as diffusion tensor imaging (DTI) validate the wounding from the brain injury.

Since HBOT has been studied as a science for over 84 years [16], a wealth of evidence exists - with or without brain imaging or functional imaging such as SPECT scans - that points to the wounding of the brain as an underlying cause of TBI and, in many cases, the cooccurrence of Post-traumatic stress disorder (PTSD). Controversy continues to wage over proper diagnoses of TBI and PTSD. The author is aware for over a decade of clinical medicine and the accumulation of "anecdotal evidence" in over 7500 successful uses of HBOT to help treat and heal TBI, that those combat veterans presenting with "PTSD only" diagnoses from the VA are overwhelmingly afflicted with undiagnosed TBI. Researchers have not yet fully understood how TBI commonly affects the neurological and clinical presentation of PTSD [17]. Despite this high prevalence, the pathogenesis of TBI, PTSD and TBI/PTSD remains largely unknown, hindering prevention and treatment efforts [18].

No matter how acquired, TBI in a veteran or a civilian, is an injury to the brain tissue. Damage is physiological, behavioral, and emotional. Symptoms can include altered consciousness; headaches; structural damage to brain matter and blood vessels and nerves; loss of neurological function that can lead to loss of motor, sensory, coordination, balance, vision, hearing and other abilities; inability to multi-task, slowed reaction time, decreased attention and concentration, inability to think fast; and frequent incapacity to work, sleep, relax, think or discern what is normal. When wounded, the brain, like all body organs, responds with the inflammatory process which proceeds to form scars, scar tissue, and chronic wounds. When the brain injury is compounded by post traumatic stress disorder (PTSD) the victim is subjected to hyperarousal, avoidance behaviors, trauma re-experiencing, increased mental vigilance, difficulty falling asleep, nightmares, constant anxiety resulting from progressive sleep deprivation and elevation of injurious stress hormones. Behaviors and emotions are magnified, intensifying the patient's negative responses: relationship problems, domestic violence, substance abuse, depression, criminal activity, unemployment, incarceration, homelessness, and too frequently suicide. Where the degenerative cycle can be arrested with drugs or psychological interventions, the result may be a lifetime of degraded quality of life on welfare – not only for the patient but typically for the caregiver as well.

In 2016, researchers at the Uniformed Services University of the Health Sciences in Bethesda, Md., found evidence of tissue damage caused by blasts alone, not by concussions or other injuries [19]. According to the New York Times, this could be the medical explanation for shell shock and the sequalae of psychological problems called PTSD [20]. The implications are clear: IEDs, breeching, enemy and/or friendly fire from personal weapons can lead directly to physical brain damage and the accompanying effects, many of which are diagnosed as "only PTSD."

Not to be overlooked are the complex interactions among brain injury, trauma, and physical/emotional/behavior/mental health. Psychiatrist Bessel van der Kolk, in The *Body Keeps the Score* [21], explains how trauma and its resulting stress harms us through physiological changes to body and brain, and that those harms can persist throughout life. Stress, trauma, depression, mental and physical health are so intertwined that it is hard to know the seat of the disease. The author argues that trauma is one of the West's most urgent public health issues. The list of its effects is long: on mental and physical health, employment, education, crime, relationships, domestic or family abuse, alcoholism, drug addiction. As with PTSD and TBI, whether a brain insult precedes mental health problems, it is certain that the brain and the body will suffer in time.

Several studies have looked at this downward cycle in untreated brain injuries [22] and noted a correspondence between the symptoms resulting from that brain injury and the HBOT Mechanisms of Action that work to arrest and heal the traumatic brain injury.

4. Hyperbaric oxygenation mechanisms of action

Medical studies have shown that Hyperbaric Oxygen Therapy is medicine's best way to provide oxygen to all parts of the body in the shortest period of time. Among many effects, HBOT has been shown to be effective in:

- Reducing local swelling (edema) and reperfusion injury
- Promoting wound healing
- Improving and repairing injury, by increasing oxygen delivery to damaged tissues
- Improving infection control
- Releasing nitric oxide with migration to point of injury
- Increasing the production of collagen
- Releasing stem cells with migration to area of injury
- Improving blood flow to the affected area of the brain
- Restarting stunned cellular metabolism and stunned mitochondria
- Generating blood vessel growth (angiogenesis)
- Activating stem cells 8x normal to repair neural pathways (neurogenesis)
- Decreasing markers of inflammation in the body and brain [23]

While it is uncommon to hear HBOT talked about in terms of healing wounds to the brain, the facts are now obvious: a major organ of the body is damaged. "Treatments" in the DoD and Veterans Administration for a brain-wounded population of at least 414,000 post-9/11 veterans typically resolve to rest and "a mix of cognitive, physical, speech, and occupational therapy, along with medication to control specific symptoms such as headaches or anxiety." [24] Virtually the last time TBI is referred to as a wound is when speaking of "the Invisible Wounds of War."

Brain wound healing demands that the body grow new tissue: blood vessels, connective tissue, new brain tissue. Cells have to grow and divide to form new tissue, necessitating stimulation of cells to divide and multiply. DNA must be stimulated [25]. By 2008 DNA analysts found that a single hyperbaric treatment turns on as many as 8101 genes in the 24 hours following HBOT treatment [26]. In short, "the turned-on genes are those genes that code for growth and repair hormones and the anti-inflammatory genes." [27] As already noted, HBOT is already approved for several on-label indications collectively similar as wound healing. It is worth noting that HBOT chambers are present in 1158 of a total of 3342 hospitals in the US [28].

Those chambers are primarily used for Wound Healing. For a variety of reasons, those chambers are not put to use on off-label uses of HBOT. Nevertheless, the bulk of science on animal and human patients with TBI has been collected in both hospital-based and private clinics.

Dr. Paul Harch prepared voluminous evidence on HBOT for wound healing in his arguments for recognition of DFW in 2002 [29]. More specific to TBI, Dr. Philip James, in "Head Injuries – the Curse of Life in the Fast Lane," [30] traces the development of HBOT-for-TBI research as far back as 1972 [31]. The study found that tissue oxygen levels that fight hypoxia rise with the increase in either the oxygen concentration or pressure: hyperbaric oxygenation. James writes that "*this one study* answers all the questions and objections raised about using hyperbaric oxygen treatment for patients with head injury." [32] Oddo in 2011 identified hypoxia as a culprit. Brain hypoxia is associated with poor short-term outcome after severe traumatic brain injury independently of elevated ICP, low CPP, and injury severity. Reduced brain oxygen (Pbto [2]) may be an important therapeutic target after severe traumatic brain injury [33]. Dr. Daphne Denham, the nation's premier expert on HBOT treatment of acute concussion, reported that 98% of her patients in her Fargo ND clinic [348 out of 350] treated within ten days of suffering a concussion, completely resolved their symptoms in five treatments or less [average of 2.4 treatments] [34]. The only difference in her patients and the thousands of concussed athletes in North Dakota who linger with symptoms for weeks and months using standard of care medicine [AKA "the tincture of time"] was HBOT. [NOTE: Maroon and Bost in 2011 write that nonpharmaceutical alternatives, dietary supplements and hyperbaric oxygen "may be a better first-line choice for the treatment of PCS, which has generally been underreported by both athletes and the military." [35] Of note for the CMS population is the work of Dr. Anne McKee on the connections between concussion and Chronic Traumatic Encephalopathy (CTE) [36]. "CTE is a progressive neurodegeneration clinically associated with memory disturbances, behavioral and personality change, Parkinsonism, and speech and gait abnormalities.... traumatic injury may interact additively with [Alzheimer's Disease] to produce a mixed pathology with greater clinical impact or synergistically by promoting pathological cascades that result in either AD or CTE."

Of no small importance is groundbreaking research from Washington State University. Researchers found that HBOT can halve the pain and symptoms of opiate withdrawal/detox [37].

And in current investigations of the use of HBOT to arrest and reverse the effects of COVID-19, preliminary evidence from China [38] (five cases) strongly suggests that based on the immutable science of HBOT and recent clinical application to deteriorating severely hypoxemic COVID-19 pneumonia patients, HBOT has significant potential to impact the COVID-19 pandemic. Fifty-eight patients as of this writing have been positively affected. Further, clinicians in at least five independent studies in the US using HBOT are raising the PO2 levels in patients in ICUs to the point where they avoid being put on ventilators and, in many cases, are being sent home after as few as five treatments [39].

5. Decades of science: studying HBOT to treat TBI

A review of the scientific evidence produced in both animal and human HBOT trials over the past twenty years demonstrates conclusively that Hyperbaric Oxygenation of TBI is safe and effective [40]. As early as 1977, Holbach and Wasserman demonstrated that HBOT at 1.5ata puts the most oxygen into the brains

of chronic stroke patients [41]. The overriding principle of wound healing, of course, is that the wound must have energy and oxygen to heal. Hypoxia is the most pervasive result of brain insults of all kinds, occasioned by inflammation that leads to reduced oxygen delivery to all body organs.

Following a Consensus Conference in 2008, at which it was declared that HBOT was safe [42], DoD/Army/VA researchers commenced a series of studies to discern whether HBOT was effective in treating TBI. Those studies over nearly eight years consumed over $126Million. Other studies in the private sector costing orders of magnitude fewer dollars were also conducted. To date, there have been at least seventeen peer-reviewed studies that have produced data and findings [43].

U.S. and Israelis clinical trials have provided well-structured, controlled studies demonstrating HBOT medicinal properties in mild TBI and persistent post-concussive symptoms [44]. Positive symptom scores for TBI and PTSD symptom scores for the two government-sponsored studies [45], the Army-sponsored study of Miller et al. [46], a civilian-sponsored study of Harch et al. [47], and an Israeli civilian study [48] show statistically significant improvements over baseline after HBOT treatments.

The studies involved patients with TBI who also suffered from Persistent Post-Concussive Syndrome (PPCS) for at least two years. It was highly unlikely that spontaneous recovery would occur. Five studies provide useful cross-study comparable measures. The U.S. studies used the Immediate Post-Concussion Assessment, Cognitive Testing, Rivermead Post-Concussion Questionnaire, and PTSD Checklist–Military (PCL-M) as the primary and secondary endpoint measures. Even though the Army/VA/DoD sponsored studies claim to be "sham-controlled," they are really dosing and-pressure-varying trials.

Clinical improvements in the studies were significant and consistent. Looking at dose response profiles shows that lower oxygen levels (100% O2) and lower pressures (2.0 ATA) are probably better for PTST/mTBI and PPCS symptom recovery.

Government-sponsored study authors assumed incorrectly that their control groups received inactive treatment. Yet they write; "We recognize that a sham is not inert, and we cannot completely discount the physiological effects of minimal increases in nitrogen or oxygen from pressurized room air. However, we believe it is biologically implausible that air at 1.2 ATA (equivalent to 2 m of seawater pressure) has a beneficial effect on healing the damaged brain remotely after mTBI [49]. (It is worth noting that the comment bears on relationship to the established science about the medicinal effects of low levels of either oxygen or pressure.) [50] Positive improvements from pretreatment (baseline) measures are observed in all the DoD/VA/Army and civilian studies. The measured responses to both HBO and HBA treatment groups are therapeutic, but a minimal effective dose of O2 at 1ata pressure has not been established in the hyperbaric medical literature. Thus, the use of a sham is problematic and confounding for study interpretation.

Deng and his team in a metanalysis evaluated nine studies comparing the efficacy between hyperbaric oxygen treatment and controls in traumatic brain injury patients [51]. "Brain metabolism, cognitive function, and outcome were taken into consideration. Results showed that HBO treatment significantly improved the Glasgow outcome scale (GOS) score and reduced overall mortality in patients with severe TBI compared with controls. In patients with mild TBI, HBO showed function alleviating the cognitive disorder after trauma, including memory, executive function, attention, and information processing speed." In patients with TBI, HBO showed significant improvement of Glasgow outcome scale score and reduction of overall mortality while NBO may play a favorable role in improving brain metabolism.

6. Implications of the science

For over four years, clinical and "evidence-based" medicine continue to show that HBOT is safe and effective in treating brain injuries. Objective analysis of the data from all the pivotal RCTs and crossover studies show in over 700 patients that positive improvements result from HBOT treatment protocols. And objective analyses of the studies and data reinforce the findings and the clinical evidence [52].

Dr. Wolf is a principle co-author of the first Army study. 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.... 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 .... Hyperbaric oxygen therapy for mild traumatic brain injury and PTSD should be considered a legitimate adjunct therapy if future studies demonstrate similar findings or show comparable improvement to standard-of-care or research-related treatment modalities." [53] Subsequent studies meet those criteria.

The Journal of Hyperbaric Medicine is the most prestigious journal on Hyperbaric Medicine in the world. In 2012 its editor wrote: " While we applaud good science, there comes a point.. .. of stagnation as the standard of evidence required for the blessing of organized medicine exceeds reality (where most of us live.... I feel, as do many of my colleagues, that there is sufficient clinical and research evidence to justify the use of [HBOT] as a standard-of-care treatment for [TBI] that should be reimbursed by CMS and Tricare.... I have no doubt that, over the next several years, [HBOT] will be proven beyond a reasonable doubt to be one of the most effective treatments for [TBI].... There is a preponderance of evidence now to justify the use and funding for the treatment...." [54] Wang et al. concur: "Compelling evidence suggests the advantage of hyperbaric oxygen therapy (HBOT) in traumatic brain injury. ...Patients undergoing hyperbaric therapy achieved significant improvement. ... with a lower overall mortality, suggesting its utility as a standard intensive care regimen in traumatic brain injury." [55].

The Samueli Institute wrote of DoD studies: "Results showed that both the HBO and sham procedures were associated with significant improvements in post-concussion symptoms and secondary outcomes, including PTSD (which most participants had), depression, sleep quality, satisfaction with life, and physical, cognitive, and mental health functioning.. .. these results are consistent with 2 other sham-controlled clinical trials among service members and veterans involving a range of HBOT doses. ... The most remarkable lesson of this study was the difference in clinical outcomes between the 2 chamber procedures (HBO 1.5 ATA and 'sham' air 1.3 ATA) and routine post-concussion care. ... These findings reinforce the argument that effective interventions [i.e., the current standard of care practiced by military medicine] 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 that contribute to symptom persistence, the equivalent of a negative placebo (nocebo) effect." [56].

While this research has been going on, the VA has been quietly conducting a controlled "demonstration project" to monitor the effects of HBOT for "PTSD-only" veterans. For nearly three years, first two and now five sites around the US are using HBOT to treat PTSD and TBI patients: Tulsa OK, Travis AFB, Joint Base Sam Houston, Tampa, and Fargo ND. While the numbers are small, the results are

extremely positive. 30 out of 30 patients have all shown positive medical improvement [57]. Significantly, numerous of the participants are diagnosed with TBI by the VA or have been found to have undiagnosed TBI. Either way, the overwhelming number of patients have improved significantly. These results are significant for reasons related to previous attempts to treat PTSD. The National Academies, writing in 2014 stated: "DoD and VA are spending substantial time, money, and effort on the management of PTSD in service members and veterans [$9.3Billion+ through 2014] [yet] neither department knows with certainty whether those many programs and services are actually successful in reducing the prevalence of PTSD in service members or veterans and in improving their lives." [58].

A Summary of the positive findings in the studies sponsored by DoD/VA/Army is instructive. They find that HBOT "offered statistical and in some measures clinically significant improvement over local routine TBI care." They even note the improvements in all groups when measured against the no-treatment group. Even their "expert" consultants wrote that HBOT heals brain injuries. The Army's premier researcher, Dr. Scott Miller, despite seeming to be looking for "the final nail in the coffin" of HBOT, says on the Veterans Affairs web site: "People did get better and we can't ignore those results." [59].

7. NOTE BENE: the sham and placebo controversies in HBOT

Expert commentary on the issues surrounding the HBOT "sham" revealed the fundamental flaws in the DoD/VA/Army research [60]. 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 with half the people in a drug trial to help show whether the drug being studied is more effective than an inactive "sugar pill." The results of each group are compared. [NOTE: Debate continues on whether it is possible, under the circumstances of HBOT treatment, to construct a true sham-controlled study.]

The placebo effect is very difficult, if not impossible, to prove in HBOT studies on patients suffering from PPCS that accompanies TBI. Further studies cannot ignore a placebo, but the overwhelmingly positive effects in so many, and so widely different studies, make the likelihood of a placebo unusual. [NOTE: when physiologic changes, such as both structural and functional increases in brain mass and activity are noted – as they were not in DoD/VA/Army studies, since they refuse to perform such objective science – it is impossible to ascribe the changes to the placebo effect. In numerous of the non-government published peer-reviewed studies on the use of HBOT for TBI, however, such positive transformations have been noted in the treated patients. Objective evidence of changes are shown in peer-reviewed research using such methods as SPECT scans, RightEye, qEEG, etc. Those changes can only be the effect of exposure to HBOT [61].]

A worldwide surge of challenges arose when the DoD/Army/VA studies purported to use a sham in their studies and reported that HBOT "does not work." [62] International researchers and authorities could read that both the data and the discussion in all the purported randomized controlled studies said virtually the same thing: "Both intervention groups [sham and treated] demonstrated improved outcomes compared with PCS care alone" [63] Dr. Pierre Marois spoke for many: "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." [64].

The clearest example to date that demonstrates that these gas/pressure combinations have a therapeutic effect on brain injury models is the article by Malek et al. [65] They demonstrated that HBO (100% O2) and HBA (21% O2/79% N2) were equivalent in protecting neurons after transient forebrain ischemia in the gerbil using 2.5 ATA. The role of a potential placebo effect was ruled out in this study and demonstrates the activity of HBO and HBA in a neurologic injury model.

The certainty that hyperbaric medicine begins with any increase in oxygen concentration and/or pressure is further substantiated by on-going work at the University of Wisconsin [66]. Animal studies already show a significant increase in mobilized stem progenitor cells and decrease in Inflammatory cytokines when HBOT and HBAT (room-air) are applied at pressures as low as 1.2ata. Together these findings support the likelihood of biologic activity, consubstantial with HBOT, being activated at much lower dose of hyperoxia than previously postulated. Those results, coupled with decades of experiments by the US Navy and US Air Force [67], demonstrate that the Army's and UHMS's claims that hyperbaric medicine only occurs at pressures higher than 1.4ata are fallacious. Any increase in oxygen concentration and/or pressure is a medical intervention.

The USAF TBI study used the Agency for Healthcare Quality and Research recommendations for future HBOT research for TBI. One pertinent comment was the following: "Whether placebo-controlled trials are necessary to evaluate HBOT has received a great deal of attention in discussions about HBOT. Participants on all sides of this debate make the assumption that an "evidence-based" approach implies devotion to double-blind, placebo-controlled trials without regard to practical or ethical considerations. This assumption is false. Double-blind, placebo-controlled trials are the "gold standard" for government regulators overseeing the approval of new pharmaceuticals, but not for clinical decision-making or insurance coverage decisions. Evidence-based clinical decisions rely more heavily on comparisons of one treatment to other potentially effective therapies, not to placebos." [68].

8. The economic argument in favor of coverage

In what will be a ground-breaking analysis released on Veterans' Day, November 11, 2020, The TreatNOW Coalition, building on the seminal work done in 2011 [69], will update and expand the "true cost of ownership" to the American taxpayer of untreated brain injuries. Most studies attempting to estimate costs typically pay attention to the obvious cost categories – drugs, yearly health care costs, ER visits, hospitalizations, psychiatric care, home health care, long term care, lost wages, and sometimes even the impact on the family. TreatNOW has gone much further in examining the "ripple effect" through the family and into society.

The Study looks at impact on the family in categories such as physical and mental damage to immediate family members, including children and care-givers; social services for children affected by turmoil; and spousal suicides occasioned by violence and abuse. Divorce, homelessness, drug abuse, incarceration, death-by-cop, and the estimated 135 people seemingly affected with every suicide [70].

A major "cost" to society beyond the medical expenditures are the tax implications of taking a brain-wounded citizen out of the work force. In too many cases, that actually equates to two lost incomes and taxes because a care-giver is typically a full-time aide to the wounded.

Brain Injury Facts about veterans are hard to pin down accurately since there are so much missing data. For example, the VA estimates that 70% of veterans are not part of the VA system. The VA also estimates TBIs alone for the period of 2000–2017 is over 414,000. RAND estimates that about one-third of all returning vets reported

symptoms of some mental health or cognitive condition. More recent estimates range up to 800,000+ for post-9/11, and an equal number of living veterans from service in the 20th century. Civilian casualties are estimated by the CDC as 2.5 million per year, with more than 5 million American effectively unemployable and unable to perform activities of daily living.

To summarize a much more robust analytical picture: untreated brain injuries cost billions of dollars each year when many of them could be reversed by application of HBOT to help heal the underlying and frequently ignored or misdiagnosed brain injury. It costs somewhere between $40,000 and $60,000 per year for each brain injured patient. HBOT treatment has shown an 85% probability of making a significant contribution to the health and welfare of treated patients, at a cost of approximately $20,000. Thus, for less than 2% of the costs of sustaining the brain wounded on welfare, those brain injuries could be treated. The possibility of returning Quality of life and independence to a significant fraction of those wounded is high.

9. Coverage with evidence

Should further research be required before HBOT for TBI receives an indication, the Center for Medicare and Medicaid (CMS) issued Guidance for the Public, Industry, and CMS Staff, Coverage with Evidence Development, November 20, 2014 [71]. CMS and AHRQ declared that the principal purpose of the study would be to test whether the item or service (HBOT for TBI) meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects. Unsurprisingly, the data and the demographics support immediate use of HBOT.

10. Conclusion

It has been the experience of independent scientists over the last decade that peer-reviewed evidence from around the world attests to the safety and efficacy of HBOT in treating and helping to heal TBI and other neurological disorders. Yet the bulk of research on brain diseases and injury focuses on description and causes rather than treatments. Research into "treatments" is by design focused on treating symptoms. Clinical Practice Guidelines from the VA/DoD, for example, specifically focus on the "management" of concussion/mild traumatic brain injury [72]. Their CPG is a compendium of best practices for dealing with symptoms, not with healing or curing. No mention is made in the document of the wound to the brain, nor to healing that wound. And none of the treatments listed as standard of practice are approved by the FDA for treating TBI [73].

Unsurprisingly, huge sums are being poured into worldwide research, some coordinated, most in a competitive surge to devise better ways to understand the structure, function, aberrations and diseases, and treatments for the brain. The US (the Brain Initiative), Europe (Human Brain Project), Japan (Brain/MINDS Project), China (Brain Project), Israel, Australia and Canada have funded major projects [74]. Groups like One Mind and Paul Allen's Brain Institute are exploring how the brain works and what causes neurological disorders. While the projects vary slightly in their aims, the thrust is on knowledge rather than clinical medicine and healing. Longer-term goals of course include medicine to the patient. Yet precious little in all the efforts is being done to find immediate-use methods to intervene in areas of wide and profound importance to human mental health.

On a more mundane basis, federal, state, local, public and private efforts continue year-after-year to address in conferences and papers and legislation the perennial, interrelated issues of suicide, mental health, brain injury, addiction, and neurocognitive and neurological decline. It is hardly surprising that the expenditures promise phenomenal rewards for breakthroughs. Meanwhile, billions are expended treating symptoms of underlying brain damage that the science demonstrates is both treatable and potentially reversible, not later, but now.

Wright and Figueroa summarize for the majority of researchers on the use of HBOT to treat and help heal TBI: "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." [75].

It is time to recognize the worldwide body of data, reduce healthcare costs, improve the lives of millions of brain-wounded and their families, and avoid lifetimes of lost earnings and the social impact of avoidable suffering. HBOT should be endorsed for the treatment of Traumatic Brain Injury. This can be achieved by extending CMS coverage to this diagnosis.

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traditionally misunderstood in terms of respiratory metabolite effects with a transient hyperoxemia that dissipates once the patient leaves the chamber. However, for 358 years, and especially in the modern era (1960 to present), permanent and later trophic effects of HBOT have been documented with both single and repetitive HBOT. [3] One of the mechanisms of action was recently elucidated as epigenetic modulation through direct effects of hydrostatic pressure and hyperoxia of gene expression/suppression of over 40% of the protein-coding genes in the human genome. The largest clusters of upregulated genes are the growth, repair, cell signaling, and anti-inflammatory genes, and the largest clusters of down-regulated genes are the pro-inflammatory genes and those that control programmed cell death. A single HBOT has been shown in multiple studies to have dramatic persisting effects on disease pathophysiology, especially inflammation, its ubiquitous acute form, reperfusion injury (e.g., carbon monoxide poisoning, necrotizing infection, resuscitation, and others), and extreme forms of acute respiratory distress syndrome (ARDS) and on reversing the lethal oxygen debt from cardiac arrest. In the Chinese COVID-19 patients HBOT was likely treating pulmonary and systemic hypoxia, inflammation, other pulmonary pathophysiologic targets, reversing oxygen debt, and modulating gene expression both acutely and durably as evidenced by the patient's sustained improvement with each daily HBOT." These are similar processes experienced in use of HBOT to treat TBI, yet another substantiation of HBOT Mechanisms of Action. Ironically, the "Chinese physicians replicated an historical experience with HBOT in a near identical pulmonary viral pandemic, the Spanish flu pandemic of 1918. Dr. Orval Cunningham of Kansas City, USA applied hyperbaric oxygen therapy (pressure and oxygen) to a moribund cyanotic Spanish flu patient with agonal breathing who experienced the same dramatic reversal of his disease that the Chinese physicians witnessed. "See: Zhong X, Tao X, Tang Y, Chen R. The outcomes of hyperbaric oxygen therapy to retrieve hypoxemia of severe novel coronavirus pneumonia: first case report. Zhonghua Hanghai Yixue yu Gaoqiya Yixue Zazhi. 2020. doi: 10.3760/cma.j.issn.1009-6906.2020.0001; Zhong XL, Niu XQ, Tao XL, Chen RY, Liang Y, Tang YC. The first case of HBOT in critically ill endotracheal intubation patient with COVID-19. Beijing, China: Novel Coronavirus Pneumonia Research Network Sharing Platform of China Association for Science and Technology. 2020; Jain KK. Textbook of Hyperbaric Medicine. 6th ed. Cham, Switzerland: Springer. 2017; Rogatsky GG, Shifrin EG, Mayevsky A. Acute respiratory distress syndrome in patients after blunt thoracic trauma: the influence of hyperbaric oxygen therapy. Adv Exp Med Biol. 2003;540:77-85; Sellers LM. The fallibility of the forrestian principle. "semper primus pervenio maxima cum VI". Laryngoscope. 1964;74:613-633.

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