Hyperbaric Oxygen (HBO) Therapy:

Changing the Treatment Paradigm for Mild Traumatic Brain Injury (mTBI), Concussion, and Related Injuries

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EXECUTIVE SUMMARY

There is a burgeoning volume of published evidence documenting the value of hyperbaric oxygen (HBO) therapy for treatment of neurological conditions, particularly mild traumatic brain injury (mTBI), concussion, and related injuries. With this solid and ever-strengthening foundation, HBO, also known as HBOT, is on the rise for these indications in the United States, where it has been used mostly to treat acute and chronic wounds (Figure 1). Basic research as well as clinical trials and case studies verify that HBO can safely initiate a cellular and vascular repair mechanism effective for neurological purposes, which supports the case for changing the treatment paradigm in the US.

Wound Care Centers in the United States With Hyperbaric Oxygen Chambers

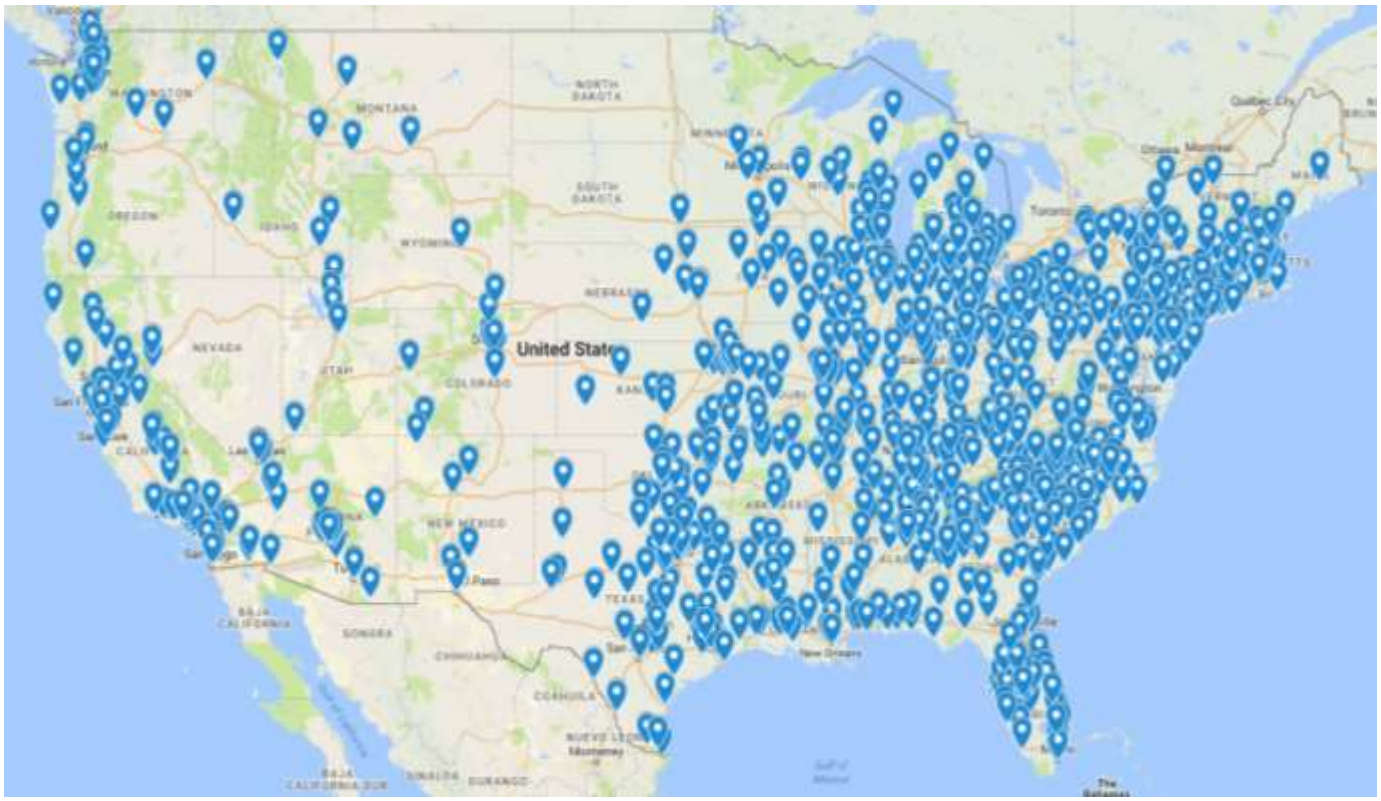

Figure 1

Source: *American Hospital Directory 2018*

The growth of hyperbaric oxygen as an adjunctive or even a primary therapy for mild traumatic brain injury (mTBI) is grabbing attention as this condition is a leading cause of chronic behavioral and cognitive disability, including dementia. In the US alone, 2.8 million people sustain a TBI annually, with 70% - 90% of cases considered to be mild. This is a significant factor as research suggests that HBO can help treat mTBI, and while use of this therapy for neurological conditions is in early stages in the US, countries such as Israel, Germany, Japan, and others routinely turn to HBO therapy as a standard practice (Table 1).

Number of HBO Treatable Diagnoses in Several Countries

Country	Number of Treatable Diagnoses
China	65 (with 18 investigational diagnoses)
Japan	20
Russia	71

Table 1

Source: *The Oxygen Revolution 2016*

Understanding why it is time to change the treatment paradigm in the US to include HBO therapy for mTBI and related neurological injuries entails:

- Explaining how HBO works
- Reviewing up-to-date evidence from the extensive research in mTBI, concussion, and stroke
- Describing why changing the paradigm is particularly promising for active and retired military veterans and athletes, especially football players who have limited treatment options and want to return to pre-injury activity levels

► The Science Behind HBO

The body of research on the subject of HBO is vast and ranges from its role in chronic wound care and related infections to decompression sickness in scuba divers, and more recently, to its use in neurological disorders. In an HBO environment, increasing pressure causes more oxygen to dissolve in the plasma, which maximizes oxygenation of the tissues. Such changes in tissue oxygenation drive a number of well-defined biochemical and molecular mechanisms, such as up-regulation of glutamate metabolism and down regulation of apoptosis.

Acceptance of this treatment for TBI, concussion, and related brain injuries is expanding as it is widely understood that the brain uses more oxygen than any other part of the body—an estimated 20% of the total body oxygen. And at any given time, the brain is utilizing almost all oxygen delivered to it. With its thin vessels, oxygen transport in the brain is very rapid, so if the brain cannot receive oxygen, it quickly goes into deficit mode.

How is HBO defined?

- HBO is a treatment delivered in a chamber and has two components: Increased total atmospheric pressure and partial pressure of oxygen that exceed ambient total pressure and oxygen partial pressure.

- HBO is a treatment with hyperbaric pressure *and* hyperoxia for disease processes whose primary targets are oxygen- and pressure- sensitive genes.

- The increased atmospheric pressure and hyperoxia function as drugs.

HBO enables wound-healing by influencing the expression of thousands of genes. The main gene actions are upregulation of trophic and anti-inflammatory genes and down-regulation of pro-inflammatory and apoptotic genes. Gene combinations affected are a function of the varying mixtures of total pressure and pressure of oxygen, triggering the healing of brain cells.

► Up-to-Date Evidence From Ongoing Research

One of the most frequent comments in the literature is the need for more well-controlled, randomized clinical trials to document the value of HBO for neurological purposes. The data generated by those trials will play a pivotal role in convincing the medical community of the safety and efficacy of HBO, laying the groundwork for ultimately changing the treatment paradigm.

As part of this effort, the May 2018 listings in clinicaltrials.gov identify 16 clinical trials for TBI, which are either recruiting, active but not recruiting, or completed (Table 2). Of these trials, five are focused directly on mTBI. Eight of the same studies also appear under the category of “Concussion” or “Post-concussive symptoms” - PCS). These studies tend to be small, and sometimes randomized and placebo-controlled (Appendix).

Clinical Trials for TBI and Concussion*

Brain Injury	Studies Recruiting	Studies Active But No Longer Recruiting	Studies Completed	Randomized?	Comments
TBI	5	1 In addition: • 1 study is not yet recruiting • 1 study is "enrolling by invitation"	8	11	- 1 study in Phase III - 7 studies in Phase I or Phase II - 4 studies are exclusively for a military population - 5 studies mention mTBI specifically
Concussion	3	1	4	5	- 1 study in Phase III - 4 studies in Phase I or Phase II - 4 studies are exclusively for a military population

* Current as of May 2018

Table 2

Source: *clinicaltrials.gov*

The foundation for current trials is rooted in earlier studies, which explored the value of HBO therapy, often measuring neuropsychological functions and brain activity, as visualized by single photon emission computed tomography, an imaging technique known as SPECT. Quality of life (QOL) evaluation has also been a common endpoint.

One particularly compelling study was a prospective, randomized, controlled trial published in 2013, which demonstrated significant preservation of neurological function in brain tissue thought to be chronically damaged *years* after initial injury. Hypothesizing that high levels of oxygen could reinvigorate dormant neurons, the researchers randomized 59 post-stroke patients into two groups: the treatment group, which was evaluated at baseline and after two months of HBO therapy; and a group that received no treatment for two months, followed by two months of HBO. The analysis of brain imaging showed significantly increased neuronal activity after a two-month period of HBO treatment compared to control periods of non-treatment. The results indicated that HBO can lead to significant improvement in brain function in post stroke patients even at chronically late stages.

Newer cutting edge work, still in the animal stage, focuses on use of HBO therapy as an inducer of glutamate oxaloacetate transaminase (GOT), a new therapeutic target in protecting against ischemic stroke injury. That GOT can enable glutamate— a neurotoxin—to assume a survival role is a paradigm shift in the role of glutamate during mTBI and stroke. Basic research using rat models indicates that the upregulation of glutamate oxaloacetate transaminase (GOT) in the presence of HBO seems to correct stroke-induced hypoxia.

► Changing the Paradigm

The science is there. With a growing volume of publications documenting the positive impact of HBO therapy, evidence is mounting in favor of changing the paradigm to include it as either adjunctive or primary treatment for neurological conditions, such as mTBI, and concussion. Making this change is particularly relevant for athletes and to members of the military who have sustained head injuries.

Football organizations at all levels, from high school to college to professional players in the NFL, have pegged safety as a top priority, a dramatic change from the days of players with injuries quickly returning to the field. As evidence that brain injuries are a serious problem, injury data released from by NFL in January 2018 show 291 concussions in the preseason, regular, and post-seasons in 2017, a 16.4% rise from 2016.

Early psychoeducational interventions continue to enjoy strong support as post-mTBI interventions, particularly consultation with psychologists or neuropsychologists, telephone-based early educational intervention and bed rest in the acute recovery phase. Also, a quick web search shows that diuretics, anti-seizure drugs, and coma-inducing drugs are sometimes used. But, these traditional approaches do not offer what HBO can do.

With anecdotal stories growing in volume, coupled with results from formal clinical trials, scientifically proven methods of healing the brain with the use of HBO are here, and are useful in minimizing or reversing damage caused by traumatic brain injury. At this time, there are considerable data to justify making HBO therapy a standard of care in the US as it provides a favorable environment by which neuronal reactivation can occur, bringing much needed help and hope to patients across the globe.

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► Introduction

The use of chambers with increasing atmospheric pressure as a medical treatment is a centuries-old practice[1,2] and is the forerunner of today's widespread use of hyperbaric oxygen (HBO) therapy for an array of health conditions. In the United States, HBO therapy, also known as HBOT, is used mostly to treat acute and chronic wounds (Figure 2)[3], and some infections, but with the burgeoning volume of published evidence documenting its value for neurological conditions, particularly mild traumatic brain injury (mTBI), concussion, and related injuries, HBO use is on the rise. Basic research as well as clinical trials and case studies document that HBO can safely initiate a cellular and

Wound Care Centers in the United States With Hyperbaric Oxygen Chambers

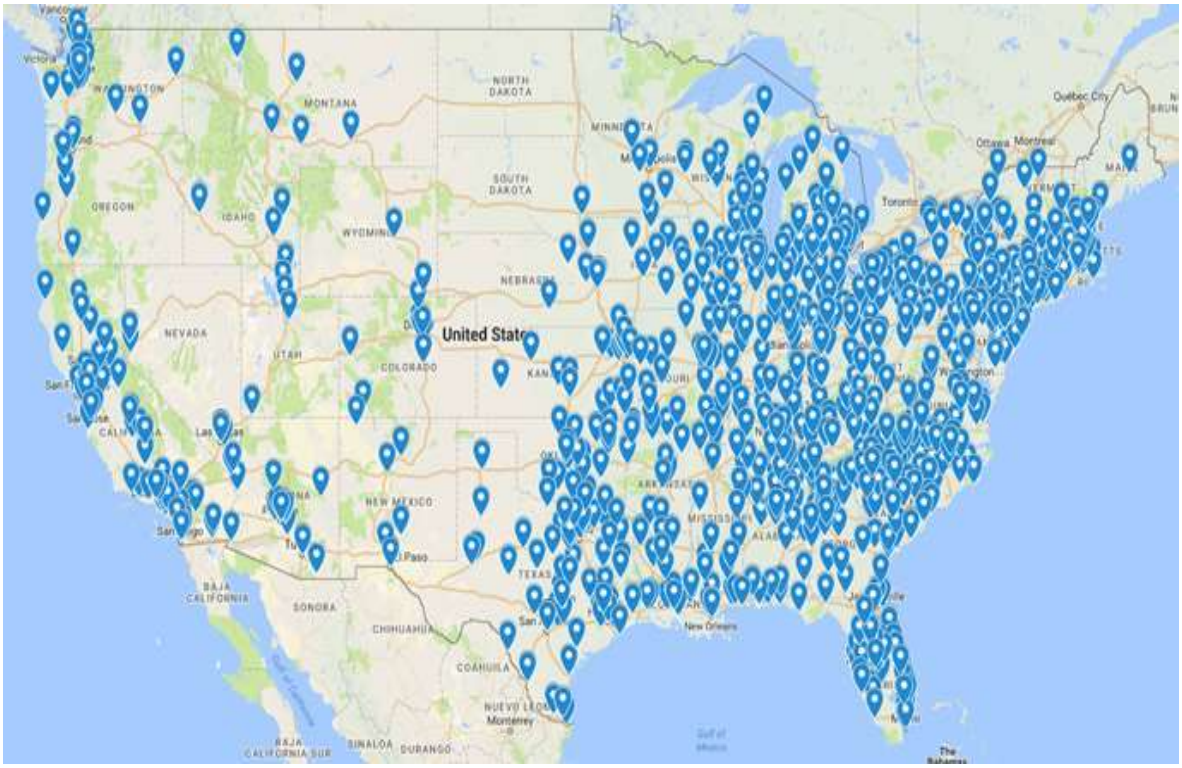

Figure 2

Source: *American Hospital Directory 2018*

vascular repair mechanism in the brain, a key factor that supports the case for changing the treatment paradigm in the US.

The growth of hyperbaric oxygen as an adjunctive or even primary therapy for mTBI is happening because this condition, a leading cause of chronic behavioral and cognitive disability, including dementia[4], has become a major public health issue. In the US alone, 2.8 million people sustain a TBI annually[5], with 70% - 90% of cases considered to be mild.[6] This is a significant finding as research suggests that HBO treatment is effective for mTBI, including the 10% - 25% of patients with prolonged post-concussion syndrome (PCS)—a group of symptoms following mTBI leading to persistent cognitive impairment.[6,7] Also benefiting from HBO therapy are patients who suffer a concussion or stroke. While use of HBO to treat these conditions is in early stages in the US, countries such as Israel, Germany, Japan, and others routinely turn to HBO therapy as a standard practice (Table 3)[8].

Number of HBO Treatable Diagnoses in Several Countries

Country	Number of Treatable Diagnoses
China	65 (with 18 investigational diagnoses)
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Table 3

Source: *The Oxygen Revolution 2016*

To understand why it is time to change the treatment paradigm in the US to include HBO as therapy for mTBI, concussion, and related injuries, this white paper will:

- Present the science behind how HBO works
- Give an up-to-date overview of the extensive research in mTBI and other neurologic conditions. This will include a table of the ongoing clinical trials using HBO as adjunctive therapy for these conditions
- Describe why HBO is particularly promising for active and retired military veterans and athletes, especially football players who have limited treatment options and want to return to pre-injury activity levels.

► A Scientific Look at Hyperbaric Oxygen Therapy and Its Benefits

There is a vast body of research on the subject of HBO, ranging from its role in chronic wound care and related infections to decompression sickness in scuba divers, and more recently, to its use in neurological disorders. In an HBO environment, increasing pressure causes more oxygen to dissolve in the plasma, which maximizes oxygenation of the tissues.[9] Such changes in tissue oxygenation drive a number of well-defined biochemical and molecular mechanisms, such as up-regulation of glutamate metabolism and down regulation of apoptosis. According to Dr. Paul Harch of Louisiana State University and the Harch Hyperbaric Institute, "Based on the accumulating numbers of scientific studies, it has been acknowledged repeatedly, particularly from 2015 to 2018, that the wound repairing growth of new tissue induced by HBO is due to the up- and down-regulation of more than 40% of all of the genes in human DNA."

Acceptance of this treatment for TBI, concussion, and related brain injuries is expanding as it is widely understood that the brain uses more oxygen than any other part of the body—an estimated 20% of the total body oxygen. And at any given time, the brain is utilizing almost all oxygen delivered to it.[6] With its thin vessels, oxygen transport in the brain is very rapid, so if the brain cannot receive oxygen, it quickly goes into deficit mode. Chandan Sen, Ph.D. Executive Director of The Ohio State University Comprehensive Wound Center, explains, "Without oxygen, every minute you wait pushes the brain cells to the point of no return."

To appreciate the benefits of HBO and understand the science behind it, defining this therapy is a critical first step. HBO is a treatment delivered in a chamber, and as explained by Dr. Harch, it has two components: increased total atmospheric pressure and partial pressure of oxygen that exceeds ambient total pressure and oxygen partial pressure.[10,11] Ambient atmospheric pressure is generally referred to as one atmosphere absolute (1ATA).

In a 2013 publication, Harch comments that frequently, HBO is mischaracterized as a treatment for diseases based on the increased oxygen component alone (>1.4 ATA oxygen).[11] Rather, it is a treatment with hyperbaric pressure *and* hyperoxia for disease processes whose primary targets are oxygen- and pressure-sensitive genes. The increased atmospheric pressure and hyperoxia function as drugs. The growing acceptance of this dual component action is leading to significant improvement in tissue

oxygenation, and subsequently, to improved clinical outcomes for neurological disorders discussed in this white paper.

There are various definitions of these conditions (Chart 1),[12,13,14,15] depending upon the therapeutic area. Sometimes, the terms are used interchangeably, with “concussion” more often used in a sports context, and “mTBI” being the preferred term in other medical specialties.[16]

Definitions

- **Mild Traumatic Brain Injury** (mTBI)

  American Congress of Rehabilitation Medicine:

  A traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

  1. Any period of loss of consciousness
  2. Any loss of memory for events immediately before or after the accident
  3. Any alteration in mental state at the time of the accident (i.e., feeling dazed, disoriented, or confused)
  4. Focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed:
     - Loss of consciousness of approximately 30 minutes or less
     - After 30 minutes, an initial Glasgow Coma Scale (GCS) of 13–15
     - Post-traumatic amnesia not greater than 24 hours

  Centers for Disease Control and Prevention

  A disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head or a penetrating head injury.

- **Concussion**

  American Association of Neurological Surgeons:

  A clinical syndrome characterized by immediate and transient alteration in brain function, including alteration of mental status and level of consciousness, resulting from mechanical force or trauma.

  Centers for Disease Control and Prevention:

  A type of traumatic brain injury—or TBI—caused by a bump, blow, or jolt to the head or by a hit to the body that causes the head and brain to move rapidly back and forth.

Chart 1

The Food and Drug Administration has adopted the Undersea & Hyperbaric Medical Society's list of indications with sufficient evidence to support HBO use.[17] These include treatment for air or gas embolism, decompression sickness, necrotizing soft tissue infections, and more[18,19] (Chart 2). Typically, these conditions have few successful therapies, plus morbidity and mortality associated with their treatment failure are significant. Consequently, HBO is a meaningful alternative for these indications, with recommended prescribed pressures in the 1.4 - 2.5 ATA range for up to 120 minutes.[20]

Current Approved Uses of HBOT

- Acute traumatic ischemias
- Air or gas embolism
- Blood loss anemia
- Bone infections (osteomyelitis) that have not improved with other treatments
- Carbon monoxide poisoning
- Decompression sickness (for example, a diving injury)
- Gas gangrene
- Idiopathic sudden sensorineural hearing loss
- Intracranial abscess
- Necrotizing soft tissue infections
- Radiation injury (for example, damage from radiation therapy for cancer)
- Skin grafts
- Thermal Burns
- Wounds that have not healed with other treatments (i.e., foot ulcer in someone with diabetes or poor circulation)

Chart 2
Source: *Undersea & Hyperbaric Medical Society 2014*

HBO works by enabling wound-healing by influencing the expression of thousands of genes. The main gene actions are upregulation of trophic and anti-inflammatory genes and down-regulation of pro-inflammatory and apoptotic genes.[10] The gene combinations affected are a function of the varying mixtures of total pressure and pressure of oxygen, triggering the healing of brain cells. HBO treatment leads to an increased number of stem cells migrating to sites of brain injury, promoting the growth of new blood vessels in the brain, and boosting the activity of mitochondria, which provide energy to cells throughout the body.[21]

To understand how TBI can be improved by HBO, research has elucidated specific mechanisms that work in parallel, or together, to induce neuroprotection in the brain. They include:[22]

1. Increasing tissue oxygenation
2. Reducing inflammation
3. Decreasing apoptosis
4. Reducing intracranial pressure
5. Promoting neurogenesis and angiogenesis

These mechanisms are critical to reversing the primary pathophysiologies of TBI, such as ionic shifts, abnormal energy metabolism, diminished cerebral blood flow, and impaired neurotransmission.[23] In the case of mTBI, HBO treats the cells affected by the injury that fail to recover on their own, and without treatment, may degenerate or die.

Understanding the neurometabolic cascade of brain injury is the result of extensive work with animal models, dating back to the 1960s. Using rat models, various studies discovered that HBO had a neuroprotective effect in experimental brain injury.[22] This research was followed by additional studies in rats as well as dogs, aimed at improving mortality, brain edema, intracranial pressure, and cerebral blood flow. An article by Hu et al details a whole host of animal studies that explored the neuroprotective effective of HBO, ranging from starting treatment in rats three hours after injury to measure decreased apoptosis, to administering HBO to rats six hours post-TBI to test for decreased apoptosis and improved cognition.[22] The review showed that HBO

demonstrated neuroprotective effects in both acute and chronic phases of TBI. Hu et al concluded that collectively, the animal studies affirmed the role of angiogenesis and neurogenesis in function improvement and provided perspective for use of HBO as an effective clinical strategy for treating TBI even at a chronic stage. They noted, however, that more clinical trials are needed to better establish the efficiency of HBO in humans.

In later work, the neuroprotective effects of HBO therapy were demonstrated during the acute phase, i.e., within 24 hours of the TBI. There are a host of studies with animal models and in humans in which the time windows for treatment were investigated. In several, researchers also compared the outcome of multiple HBO treatment sessions versus single sessions. In one study by Wang et al, a Sprague-Dawley rat model explored whether multiple sessions extended the therapeutic window [24] Researchers found that the onset of HBO treatment at 3, 6, or 12 hours significantly reduced neurology deficit scores and brain water content ($p < 0.01$), but there was no discernible effect for these two variables when HBO treatment was launched 24, 48, or 72 hours after TBI. By comparison, multiple sessions (60 minutes; three or five treatments in all), even administrated up to 48 hours post-TBI, significantly reduced overall neurological deficit scores and neuronal apoptosis as compared to a single session. Compared with the control group, three and five treatments reduced neurology deficit scores ($p < 0.01$), and increased the number of neurons ($p < 0.01$). Wang et al concluded that HBOT after TBI can exert significant neuroprotective effects.

Translating this scientific background into clinical practice is happening as evidenced by the growing number of case studies in the literature and websites detailing anecdotal success with HBO for neurological disorders. One notable website is TreatNOW (treatnow.org), which has a mission of "identifying and treating veterans and others suffering from concussion/TBI/post-traumatic stress disorder". This is vital work as TBI is a widely acknowledged problem in the military, with blast injury the most common cause of war injuries and death[25]. Articles in the lay press are highlighting the expanded use of HBO to treat these injuries, notably for military personnel, and in addition, there are a raft of articles detailing anecdotal information on how professional football players suffering from TBI are benefiting from HBO. The sidebars describe one sports case study[26], and one military case study[27], with each explaining the effectiveness of HBO as measured by various neurological evaluations.

NFL Case Study Documents
Effectiveness of HBO

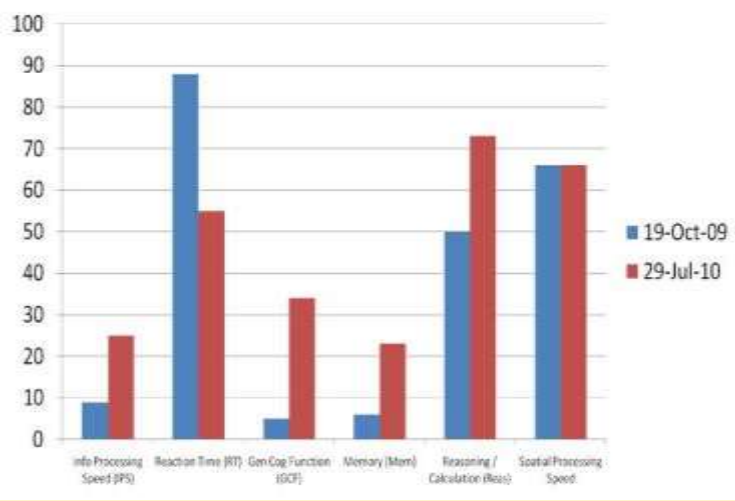
A retired NFL player was first hospitalized with a TBI resulting in loss of consciousness during a tackling drill.

He experienced numerous minor concussions over the years, but his second major concussion occurred during the first play for his NFL team early in the first quarter. He went through 25 to 30 smelling salts in order to finish the game. He had no recollection of participating in that game, but was sent back on the practice field the very next day.

Early in his second season (1981), he developed hydrocephalus, and underwent emergency shunt brain surgery. Four months after his team won Super Bowl XVI, his shunt failed, and he had back-to-back emergency brain surgeries and was given last rites. By 1990, he had nine more shunt revisions.

He received 40 HBO sessions at 1.5 times ATA, lasting 60 minutes each (one treatment per day - 100% oxygen). He was independently followed with neurocognitive evaluations and single-photon emission computerized tomography (SPECT) brain imaging. He had a marked improvement in five out of six indices on the MicroCog Assessment conducted after the 40 HBO sessions.

Note: A lower score on Reaction Time is a better result.



Source: *K.P. Stoller, 2011, Medical Gas Research*

Military Case Study Documents
Effectiveness of HBO

Two military vehicle operators were driving when their vehicle was attacked by an improvised explosive device. Both suffered concussions, and although symptoms initially seemed mostly resolved several weeks later, they began to suffer headaches and had trouble sleeping. In addition, they felt they were quick to anger and remained so for long periods of time, even for trivial matters. They also had trouble focusing on details, and were forgetful and frequently tired.

Both had received the Automated Neuropsychological Assessment Metrics test (ANAM) two months prior to the injury and both received the test again six months post-injury. The second testing showed marked declines from the pre-injury baseline in both men in areas such as simple reaction time, procedural reaction time, and matching to sample. Some changes were statistically significant, and both were diagnosed with mTBI.

Because the two airmen showed no improvement in their symptoms for seven months and were having difficulty performing their jobs, both began HBO eight months after the injury. The treatment protocol was 100% oxygen for one hour at 1.5 ATA, given five days per week. Clinical improvement was rapid. Airman #1 reported that his headaches vanished by the fifth treatment and did not return, and he was able to sleep seven to eight hours per night uninterrupted. Airman #2 reported that his headaches weakened to 3-4 on a pain scale of 1-10, lasted only one to two hours instead of the previous eight to 10 hours, and that he was able to sleep eight to nine hours per night uninterrupted. Both airmen stated that they felt more mentally alert and were less prone to forgetting, although they still did not feel "normal."

Repeat ANAM testing showed improvement in essentially all areas for both airmen. Airman #1's ANAM scores returned to pre-injury baseline levels, and he was considered well and able to return to full duty. Airman #2 ANAM scores returned to pre-injury levels, with no statistically significant differences in any of the tested domains, but cognitively, there were still deficits. This led to his receiving an additional 40 HBO treatments. Results showed improvement in all measures at or exceeding his pre-injury state, except for matching to sample, which still improved substantially from the injury state.

Source: *Wright et al, 2009, Undersea and Hyperbaric Medical Society*

Finally, with increased attention paid to head injuries in football, escalating all the way to the National Football League (NFL), it is noteworthy that in January 2018, the league announced its $17 million commitment to the funding of research into concussions and the effects of brain injuries. As described in a recent article in *The Washington Post,* the funding will be divided amongst research by the Department of Defense, TRACK-TBI (a study funded by the National Institutes of Health) and the National Institute on Aging, a branch of the NIH.[28] This funding is part of its $30 million commitment to NIH from 2012 to fund the Sports and Health Research Program, whose goal is to accelerate research that enhances the health of athletes, and ultimately the military and the general public. Its initial focus was TBI, as 20% of those injuries with loss of consciousness are sports- or recreation-related.[29] Also included is chronic traumatic encephalopathy (CTE), a degenerative brain disease, often resulting from multiple concussions that can lead to lasting structural changes in the brain.

With all of these factors aligning – research into brain injury, greater insight into how HBO therapy works and anecdotal case studies of its benefits, plus government funded initiatives and public-private collaborations—this is the right time to consider greater use of HBO as integral to the treatment paradigm.

► An Up-to-Date Overview of HBO Research

The mechanism of how HBO therapy treats brain injury continues to be a heavily researched area, with particular interest in this modality for helping athletes and members of the military. Many published case studies, case series, and numerous online videos provide anecdotal evidence of its value.[8] In addition, ongoing animal work has researched biochemical pathways that link HBO to neurological improvement. Still, a frequent comment in the literature is that more well-controlled, randomized clinical trials are needed to build clinical evidence and strengthen the case for its widespread use. Fortunately, more are underway.

As of May 2018, clinicaltrials.gov lists 16 clinical trials for TBI, which are either recruiting, active but not recruiting, or completed (Appendix). Of these trials, five are focused directly on mTBI. Eight of these same studies are listed under “Concussion” or “Post-concussive symptoms” - PCS. For both conditions, these studies tend to be small, and sometimes randomized and placebo-controlled (Table 4).

One example of a study listed in both the mTBI and concussion categories is an active Phase III trial entitled *Hyperbaric Oxygen Treatment to Treat Mild Traumatic Brain Injury (mTBI)/Persistent Post-Concussion Syndrome (PPCS*)”.[30] This randomized study, looking to enroll 59 participants, uses a crossover design, including an HBO group and a non-HBO control. After eight weeks, the non-HBO group crosses over to receive the same 40 HBO treatments as the HBO group. The study provides treatments

administered once daily at 1.5 ATA, five days per week for eight weeks, and has the following primary outcome measures:

- Working memory (one week after final HBO)
- Neurobehavioral Symptom Inventory (a self-report measure of symptoms)

Clinical Trials for TBI and Concussion*

Brain Injury	Studies Recruiting	Studies Active But No Longer Recruiting	Studies Completed	Randomized?	Comments
TBI	5	1 In addition: • 1 study is not yet recruiting • 1 study is "enrolling by invitation"	8	11	- 1 study in Phase III - 7 studies in Phase I or Phase II - 4 studies are exclusively for a military population - 5 studies mention mTBI specifically
Concussion	3	1	4	5	- 1 study in Phase III - 4 studies in Phase I or Phase II - 4 studies are exclusively for a military population

* Current as of May 2018

Table 4

Source: *clinicaltrials.gov*

The foundation for current trials is rooted in earlier studies, which explored the value of HBO, often measuring neuropsychological functions and brain activity, as visualized by single photon emission computed tomography, an imaging technique known as SPECT. Quality of life (QOL) evaluation has also been a common endpoint.

One such trial, conducted in Israel from 2008 – 2012, enrolled 56 mTBI patients, up to

1 – 5 years post-injury, with prolonged PCS.[6] In addition to a QOL endpoint, this study also measured improvement in brain function through HBO using 100% oxygen at 1.5 ATA. Patients were randomized to either the treatment group, with an evaluation at baseline and after 40 HBO sessions; or to the crossover group, with evaluations at baseline, again after a 2-month control period of no treatment, and also after a two month period of 40 HBOT sessions, lasting five days per week, with each lasting 60 minutes.

There were significant improvements ($p < 0.05$) in cognitive functions and QOL in both groups following HBO, but no significant improvement following the control period. To make this determination, QOL was evaluated using an EQ-5D questionnaire, which measures descriptive activities such as mobility and depression; and self-rated health using a visual analogue scale. Changes in brain activity were assessed by SPECT imaging. The researchers concluded that HBO can induce neuroplasticity leading to repair of chronically impaired brain functions and improved QOL in mTBI patients with prolonged PCS at late chronic stage—*years after injury*.

Similarly, a prospective, randomized, controlled trial by Efrati et al, also conducted in Israel, demonstrated significant preservation of neurological function in brain tissue thought to be chronically damaged years after initial injury.[9,31] Hypothesizing that high levels of oxygen could reinvigorate dormant neurons, the researchers randomized 59 post-stroke patients into two groups. The treatment group was evaluated at baseline and after two months of HBO (40 sessions, administered five days/week, each lasting

90 minutes); and the other group, which received no treatment for two months, was evaluated at baseline, at the end of the no treatment period, and again, followed by two months of HBO, also using 40 sessions. Treatment consisted of 100% oxygen at 2 ATA. Primary endpoints were neurologic functions as evaluated by National Institutes of Health Stroke Scale, ability to perform activities of daily living, and brain metabolism as visualized SPECT.

Analysis of brain imaging showed significantly increased brain activity after a two-month period of HBO treatment compared to control periods of non-treatment. In the treated group, 55% had significant improvement after HBO and 35% had mild improvement. Specifically, in the cross group, during the first (control) period, 36% had mild improvement and only 6.2% had significant improvement ($p < 0.001$), but after HBO, the cross group demonstrated 43% significant improvement and 29% mild improvement ($p < 0.001$) Patients experienced improvements such as a reversal of paralysis, increased sensation, and renewed use of language. The results indicated that HBO can lead to significant improvement in brain function in post stroke patients even at chronically late stages, as new connections in damaged regions are built.

► GOT – A New Therapeutic Target

Some cutting edge work, still in the animal stage, focuses on use of HBO as an inducer of glutamate oxaloacetate transaminase (GOT), a new therapeutic target in protecting against ischemic stroke injury. That GOT can enable glutamate to assume a survival

role is a paradigm shift in the role of glutamate during mTBI and stroke.[32] Glutamate is the body's most abundant excitatory neurotransmitter, and under pathological conditions, it is a potent neurotoxin, and efforts to block its mechanisms of excitotoxicity have failed in clinical trials. Basic research using rat models, however, indicates that the upregulation of glutamate oxaloacetate transaminase (GOT) in the presence of HBO seems to correct stroke-induced hypoxia. How, exactly, does GOT facilitate the transformative switch of otherwise excitotoxic glutamate into intermediates during ischemic stroke?

The biochemistry behind this research is quite complex, but a simple explanation starts by understanding that the brain, which accounts for just 2% of total body weight, has tremendous energy demands. As described by Khanna et al, of Ohio State University, the majority (~60%) of aerobic oxidation of glucose in brain tissue is needed for electrical signaling linked to depolarization and repolarization of neuronal membranes.[32,33] Neurons tend to derive their energy from the oxidation of glucose, but neurons lack glycogen stores, and without glycogen, adenosine triphosphate (ATP) levels in neurons are rapidly depleted during ischemic stroke as blood supply carrying oxygen and glucose to the brain is halted. Within 10 short minutes of cerebral ischemia, ATP levels drop by more than 95%.

In researching how HBO and normobaric oxygen (NBO)* can correct ischemic stroke-induced hypoxia, Khanna et al uncovered the oxygen-dependent upregulation of GOT –

* Normobaric oxygen (NBO) - oxygen administered at 1 atmosphere.

a novel neuroprotective target. During cerebral ischemia, defined as 90 minutes of middle cerebral artery occlusion (MCAO), correction of ischemic stroke-induced hypoxia by HBO and NBO protected brain tissue from injury. This finding was observed in a study in which Wistar rats, randomized to one of four treatment groups, were subjected to 90 minutes of MCAO, HBO (100% O_2 at 2ATA) and NBO (100% O_2 at 1ATA). The stroke lesion volume was reduced by > 50% after 48 hours post-reperfusion. The opposite effect was noticed, however, when HBO and NBO were applied *afte*r 90 minutes of cerebral ischemia.[34]

As explained in a 2015 article describing this research, the concept that GOT was upregulated when stroke-induced hypoxia was corrected "led to the exciting hypothesis that GOT transamination could":

1) Enable extracellular glutamate clearance from the ischemic site
2) Feed cellular respiration to generate energy in otherwise glucose-starved, energy-deprived neurons

Regarding this research, Dr. Chandan Sen, also of Ohio State, comments, "In the case of ischemic-stroke-induced hypoxia, and in the presence of HBO, the brain can now rescue itself. This finding is striking."

This cutting-edge research is happening at the same time the volume of anecdotal case studies on the use of HBO to treat mTBI is on the rise, and more clinical trials are underway.

► The Sham Control

There are long-standing reservations by the medical establishment about the effectiveness of HBO therapy for TBI, concussion, and stroke, and in attempts to understand why, Boussi-Gross et al have identified three issues that have limited HBO acceptance:[6]

1. Lack of knowledge about the connection between metabolism and neuroplasticity
2. Lack of randomized clinical trials with standard placebo control
3. Sham control with room air at 1.3 ATA yielded significant improvement

Each of these issues is addressed by the researchers, starting with a comment on the expanding published evidence linking elevated oxygen, metabolism and brain activity to neuroplasticity. Much of their article, however, is focused on the subject of why sham control groups have sometimes yielded significant improvement.

The researchers comment that in some studies, a so-called sham is actually not a sham at all. By definition, a sham should be medically ineffective, but since the minimal pressure for a patient to sense a pressure increase is 1.3 ATA, this level of atmospheric pressure has been used as the sham. As a result, breathing regular air under hyperbaric conditions of 1.3 ATA leads to more than 50% elevation in tissue oxygenation. And because the result can be significant, 1.3 ATA is not an “ineffectual treatment”, and therefore, does not quality as a proper sham control.

Any discussion about the effectiveness of HBO requires an understanding of what a sham control should be in order to interpret study results. This topic is discussed in the literature, emphasizing how if the sham really isn't one, results and conclusions of studies comparing it to HBO are going to be mischaracterized. To be a true sham, any controlled experiment testing HBO must omit in its control groups the active ingredients, namely increased pressure and hyperoxia.[11] One published study included *both* in its sham,[35] and those researchers erroneously concluded that for treatment of mTBI/PCS and post-traumatic stress disorder, the sham was actually more effective than the treatment arm, which used HBO therapy at 2.4 ATA pressure.[6,11] But what those researchers had really conducted was a study of two different doses of HBO therapy, with both showing efficacy.

This continued mischaracterization is particularly evident in a number of trials conducted by the military. In an article by Dr. Harch on use of HBO for chronic TBI, he discusses that many civilian articles have reported success with HBO, but articles describing military-funded studies have a confusing mix of misinterpreted or indeterminate data.[10] He cites various review articles in which military-funded studies failed to acknowledge that improperly structured shams were, in fact, treatment groups. When this issue is taken into account, i.e. when studies are re-evaluated as using multiple doses of HBOT, results of Department of Defense studies align with those of civilian studies.

► How Safe is HBO Therapy?

An insightful literature review article entitled *The Inspiring Journey of Hyperbaric Oxygen Therapy, From the Controversy to the Acceptance by the Scientific Community* tracks the changing views and growing acceptance by the medical profession of HBOT use for various medical conditions.[36] In this detailed analysis, Nikitopoulou and Papalimperi describe the wide-ranging uses of HBOT, and the article concludes with the current focus on neurological dysfunction and the need for more randomized clinical trials, given today's strong emphasis on efficacy and safety.

So, how safe is HBO therapy? A pivotal article by Jokinen-Gordon et al, published in 2017, confronts this question head-on in a retrospective study using a large dataset. The research includes an analysis of 1.5 million HBO treatments, mostly for wound-related indications. Treatments were administered from 2012 to 2015 in outpatient wound care centers across the US managed by Healogics, a provider of wound care services.[20] The researchers concluded that HBOT is a safe and low-risk intervention when administered according to appropriate therapeutic protocols. Specifically, only 0.68% of the treatments were associated with an adverse event, mostly commonly barotrauma (0.37%) (otic or sinus), and confinement anxiety (0.16%) (Table 5). These findings are meaningful for physicians as concerns about adverse events influence treatment decisions.

Frequency of Adverse Events During Hyperbaric Oxygen Treatments

Event	n	Percentage	Rate/10,000	Mean Treatment Length (min)	Standard Deviation
No event	1,519,419	99.32	9,931.76	113.35	14.06
Barotrauma	5,643	0.37	36.88	64.04	51.87
Confinement Anxiety	2,436	0.16	15.92	64.27	31.88
Hypoglycemia	1,275	0.08	8.33	103.75	19.11
Shortness of Breath	739	0.05	4.83	79.72	32.30
Seizure	267	0.02	1.74	99.54	26.82
Oxygen Toxicity	79	0.01	0.52	96.04	27.68
Pneumothorax	1	0.00	0.00	-	-
Total	1,529,859	100	10.000	113.06	14.91

Table 5

Source: *Jokinen-Gordon et al., 2017*

In their research, Jokinen-Gordon et al determined that on average, the percentage of treatments with an event was associated with higher pressure-reached values. For instance, 18.8% of treatments with an event had a pressure-reached value of 2.5 ATA versus 15.2% of treatments without an event. Furthermore, treatments with event occurrence were less likely to have reached the prescribed pressure level. Also, the mean treatment time for treatments without an event was 7.7 minutes longer ($P < 0.001$) than average treatment length with an event. Treatments that included shortness of breath and confinement anxiety had the highest odds of discontinuing compared with treatment courses without an event: 2.74 [95% confidence interval, (2.01 - 4.32)] and 2.72 [(95% confidence interval, 2.36 -3.25)], respectively.

► Changing the Paradigm

The science is there. With a growing volume of publications documenting the positive impact of HBOT, evidence is mounting in favor of changing the paradigm to include it as either adjunctive or primary treatment for neurological conditions, such as mTBI, concussion, and related illnesses. From the groundbreaking work at Ohio State University on how HBOT acts as an inducer of GOT to ongoing clinical trials to completed studies that have shown statistically significant improvements in cognitive functions and QOL following HBOT, the time is now to make this therapy a standard practice in the US, as it is in other countries.

Making this change is particularly relevant for athletes and to members of the military who have sustained head injuries. Football organizations at all levels, from high school to college to professional players in the NFL have pegged safety as a top priority, a dramatic change from the days of players with injuries quickly returning to the field. Today, there is a five-step protocol that players with head injuries must complete before returning to play.[37] And as evidence that brain injuries are a serious problem, injury data released by the NFL in January 2018 show a 16.4% rise in diagnosed concussions from 2016 to 2017 during the preseason, regular, and post-seasons (Table 6).[38]

Incidence of Concussions in the NFL

Year	Preseason	Regular Season + Postseason	Totals for Pre, Regular, and Postseason
2012	85	180	265
2013	77	167	244
2014	83	129	212
2015	83	196	279
2016	71	179	250
2017	91	200	291

Table 6

Source: *National Football League 2018*

In football, there is also the issue of chronic traumatic encephalopathy, a degenerative brain disease caused by repeated hits to the head, essentially multiple concussions, Despite efforts to improve safety, this condition remains disturbingly common in football players,[39,40] and can impact mood, cognition, and behavior, such as anger and depression, as well as dementia.

Based on current findings in clinical trials and anecdotal case studies, and nearly 3 million Americans suffering traumatic brain injuries annually, the traditional treatment paradigm is no longer sufficient or acceptable. As Prince and Bruhns report, early psychoeducational interventions continue to enjoy strong support as post-mTBI therapy, a conclusion they drew based on their literature analysis, including several systematic reviews.[41] Their research, which is limited to a civilian population—not veterans or athletes—notes that these interventions typically include earlier consultation with psychologists or neuropsychologists, telephone-based early educational intervention and bedrest in the

acute recovery phase. Also, a quick web search shows that diuretics, anti-seizure drugs, and coma-inducing drugs are sometimes used.[42]

One principal investigator comments, “I am a true believer in HBO therapy. At our medical center, we get letters and e-mails from all over the world from people seeking help because their lives have been devastated. There is nothing out there like this—no pill or talk therapy is offering results similar to HBO. When I worked in wound healing centers and saw people receiving HBO therapy for wounds, such as diabetic foot ulcers, some also had strokes and neurological problems, and couldn’t speak. As we treated them for wounds in the hyperbaric chamber, some actually started to speak and experienced improvement in neurological status. Of course this is all anecdotal and more research needs to be done”.

With these anecdotal stories building in volume, coupled with results from formal clinical trials, scientifically proven methods of healing the brain with the use of HBO are here, and are helpful in minimizing and reversing the damage caused by traumatic brain injury. More well-designed, randomized, multi-center clinical trials are still needed to expand the body of literature and address skepticism in the medical community. But, at this time, there are considerable data to justify making HBO therapy a standard of care in the US, as it provides a favorable environment by which neuronal reactivation can occur, bringing much needed help and hope to patients across the globe.

Appendix: Listings on clinicaltrials.gov for mTBI and Concussion (Accurate as of May 2018)

Number	Clinical Trials Identifier	Trial Name	Status	Comments
	Traumatic Brain Injury			
1	NCT00594503	Hyperbaric Oxygen Therapy and SPECT Brain Imaging in Traumatic Brain Injury	Recruiting	Phase I, single site, interventional open label
2	NCT02089594	Hyperbaric Oxygen Treatment to Treat Mild Traumatic Brain Injury (mTBI)/Persistent Post-Concussion Syndrome (PPCS)	Recruiting	Phase III, single site, interventional, randomized
3	NCT03339037	Hyperbaric Oxygen Therapy Effect on Post Concussion Syndrome in Children (TBIPED)	Recruiting	Single site, interventional, randomized
4	NCT01986205	Hyperbaric Oxygen for Civilian Post-concussive Syndrome (HYBOBI2)	Recruiting	Phase II, multi-site, interventional, randomized
5	NCT01847755	Hyperbaric Treatment of Traumatic Brain Injury	Recruiting	Phase I, Phase II, single site, interventional, open label
6	NCT02452619	MRI Brain Changes Induced by Hyperbaric Oxygen Therapy in Brain injury Patients	Enrolling by Invitation	Single site, observational, retrospective
7	NCT02407028	Hyperbaric Oxygen Brain Injury Treatment Trial (HOBIT)	Not Yet Recruiting	Phase II, multi-site, interventional randomized
8	NCT01925963	Normative Datasets for Assessments Planned for Mild Traumatic Brain Injury (NORMAL)	Active, Not Recruiting	Multi-site, observational, prospective
9	NCT00810615	Treatment of Traumatic Brain Injury with Hyperbaric Oxygen Therapy	Completed	Phase I, Phase II, single site, interventional, randomized
10	NCT01611194	mTBI Mechanisms of Action of HBO2 for Persistent Post-Concussive Symptoms (BIMA)	Completed	Multi-site, Interventional, randomized
11	NCT01306968	Hyperbaric Oxygen Therapy (HBO2) for Persistent Post-Concussive Symptoms After Mild Traumatic Brain Injury (mTBI) (HOPPS)	Completed	Phase II, multi-site interventional randomized
12	NCT01220713	Hyperbaric Oxygen Therapy (HBO2T) for Post-Concussive Symptoms (PSC) After Mild Traumatic Brain Injury (mTBI) (HBOT)	Completed	Phase II, multi-site interventional, randomized
13	NCT00760734	Hyperbaric Oxygen Therapy (HBOT) in Chronic Traumatic Brain Injury (TBI)/Post-Concussion Syndrome (PCS) and TBI/Post-Traumatic Stress Disorder (PTSD)	Completed	Phase I, single site, interventional, open label
14	NCT00715052	The Effect of Hyperbaric Oxygen Therapy on Patients Suffering From Neurologic Deficiency Due Traumatic Brain Injury	Completed	Single site, interventional, randomized

Number	Clinical Trials Identifier	Trial Name	Status	Comments
15	NCT00170352	Comparison Between Different Types of Oxygen Treatment Following Traumatic Brain Injury	Completed	Phase II, single site, interventional, randomized, open label
16	NCT01430325	Test of Chamber Pressure to Divers and Chamber Attendants (TOP-DIVER)	Completed	Multi-site, interventional, randomized
	CONCUSSION (all of these studies appear in the TBI list)			
1	NCT02089594	Hyperbaric Oxygen Treatment to Treat Mild Traumatic Brain Injury (mTBI)/Persistent Post-Concussion Syndrome (PPCS)	Recruiting	Phase III, single site, interventional, randomized
2	NCT03339037	Hyperbaric Oxygen Therapy Effect on Post Concussion Syndrome in Children (TBIPED)	Recruiting	Single site, interventional, randomized
3	NCT01986205	Hyperbaric Oxygen for Civilian Post-concussive Syndrome (HYBOBI2)	Recruiting	Phase II, multi-site, interventional, randomized
4	NCT01925963	Normative Datasets for Assessments Planned for Mild Traumatic Brain Injury (NORMAL)	Active, Not Recruiting	Multi-site, observational, prospective
5	NCT00760734	Hyperbaric Oxygen Therapy (HBOT) in Chronic Traumatic Brain Injury (TBI)/Post-Concussion Syndrome (PCS) and TBI/Post-Traumatic Stress Disorder (PTSD)	Completed	Phase I, single site, interventional, open label
6	NCT01611194	mTBI Mechanisms of Action of HBO2 for Persistent Post-Concussive Symptoms (BIMA)	Completed	Multi-site, Interventional, randomized
7	NCT01306968	Hyperbaric Oxygen Therapy (HBO2) for Persistent Post-Concussive Symptoms After Mild Traumatic Brain Injury (mTBI) (HOPPS)	Completed	Phase II, multi-site interventional randomized
8	NCT01220713	Hyperbaric Oxygen Therapy (HBO2T) for Post-Concussive Symptoms (PSC) After Mild Traumatic Brain Injury (mTBI) (HBOT)	Completed	Phase II, multi-site interventional, randomized

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