



PERSONNEL AND
READINESS

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

JAN 29 2018

The Honorable William M. "Mac" Thornberry
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

The enclosed report is in response to Senate Report 113-44, pages 132-133, to accompany S. 1197, the National Defense Authorization Act for Fiscal Year 2014, "Hyperbaric Oxygen Therapy for Mild Traumatic Brain Injury." The report requests the Secretary of Defense to provide a report to the Senate and the House of Representatives Committees on Armed Services within 180 days of completion of hyperbaric oxygen (HBO₂) therapy pilot studies to determine the effectiveness for alleviating symptoms after mild traumatic brain injury (mTBI) in military personnel, and specifies that the report should describe the methodology, results, and conclusion of the studies. The studies were completed in August 2017.

This report describes the five Department of Defense (DoD) pilot studies for determining the effectiveness of HBO₂ therapy for alleviating symptoms of mTBI in Service members. Based on findings from the completed DoD trials, the DoD should not offer HBO₂ as an off-label or as an evidence-based therapy for mTBI. Accordingly, no policy changes relative to HBO₂ treatment of mTBI are indicated at this time. The DoD remains committed to researching, finding, and providing existing and new evidence-based treatments for mTBI for our injured Service members and their families.

Thank you for your interest in the health and well-being of our Service members, veterans, and their families. A similar letter is being sent to the Chairman of the Committee on Armed Services of the Senate.

Sincerely,

A handwritten signature in black ink that reads "Robert L. Wilkie".

Robert L. Wilkie

Enclosure:
As stated

cc:
The Honorable Adam Smith
Ranking Member



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JAN 29 2018

The Honorable John McCain
Chairman
Committee on Armed Services
United States Senate
Washington, DC 20510

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Enclosure:
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cc:
The Honorable Jack Reed
Ranking Member

**REPORT IN RESPONSE TO SENATE REPORT 113-44, PAGES 132-133,
TO ACCOMPANY S. 1197, THE NATIONAL DEFENSE AUTHORIZATION ACT OF
FISCAL YEAR 2014**

“HYPERBARIC OXYGEN THERAPY FOR MILD TRAUMATIC BRAIN INJURY”



JANUARY 2018

**SUBMITTED BY THE OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
FOR HEALTH AFFAIRS**

The estimated cost of this report or study for the Department of Defense (DoD) is approximately \$5,400 for the 2017 Fiscal Year. This includes \$1,500 in expenses and \$3,900 in DoD labor.

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1. PURPOSE

Senate Report 113-44, pages 132-133, to accompany S. 1197, the National Defense Authorization Act for Fiscal Year 2014, requested the Secretary of Defense provide a report to the Senate and the House of Representatives Committees on Armed Services, within 180 days of completion of the Department of Defense (DoD) pilot studies, to determine the effectiveness of hyperbaric oxygen (HBO₂) therapy for alleviating symptoms after mild traumatic brain injury (mTBI) in military personnel. The report should describe the methodology, results, and conclusion of the studies. Further, if HBO₂ therapy was determined to be effective, the Senate report requested that the DoD report address any changes in policy or legislation that may be needed regarding the provision of HBO₂ services to patients with mTBI.

This report describes the five DoD pilot studies for determining the effectiveness of HBO₂ therapy for alleviating symptoms of mTBI in Service members. The report is organized to address each of the Committees' concerns, and includes citations for the scientific publications resulting from each study.

2. BACKGROUND

HBO₂ therapy is a drug-device combination treatment during which a patient breathes oxygen (the drug) under increased atmospheric pressure in a hyperbaric chamber (the device) to achieve elevated oxygen levels in the blood and tissue. While any whole body exposure to pressure in excess of sea level (i.e., one atmosphere absolute [ATA]) is considered a hyperbaric exposure, the Undersea and Hyperbaric Medical Society (UHMS) defines "clinical" HBO₂ as an intervention during which an individual breathes near 100 percent oxygen while inside a hyperbaric chamber pressurized to greater than or equal to 1.4 ATA. The "dose" of oxygen received during HBO₂ therapy, defined in terms of oxygen partial pressure or ppO₂ (generally measured in ATA or millimeters of mercury [mmHg]), is a product of the absolute ambient chamber pressure and the percentage of oxygen breathed.

At present, the U.S. Food and Drug Administration (FDA) has approved the use of hyperbaric chambers to treat 13 distinct medical conditions. Similarly, the UHMS accepts HBO₂ as a treatment for 14 clinical indications. With the exception of decompression sickness and arterial gas embolism treatment, for which HBO₂ therapy is indicated as the treatment of choice, HBO₂ is considered a treatment adjunct to standard of care medical interventions for all other indications. Specific to the context of this report, HBO₂ therapy is not currently approved by the FDA, nor endorsed by third-party carriers or medical professional organizations, including the UHMS, for treatment of mTBI or persistent post-concussion symptoms (PCS). Nevertheless, citing anecdotal reports, case series, and crossover design studies, some clinicians, researchers, and advocates have called for HBO₂ therapy to be approved as a treatment for these indications. In response, and as part of its ongoing commitment to researching, finding, and providing existing and new evidenced-based treatments for injured Service members with mTBI, the DoD has sponsored four randomized, prospective, sham-controlled studies and one randomized, crossover-controlled study evaluating the effectiveness of HBO₂ therapy in alleviating Service member symptoms after mTBI. As of September 2017, the DoD's five studies have been

completed. A brief summary of each study's methodological design and the outcomes of the completed studies and meta-analysis are presented below.

3. METHODS

This section provides a brief description of the five DoD-sponsored pilot studies evaluating the effects of HBO₂ therapy on Service members with mTBI. The appendices provide citations for the resultant peer reviewed publications associated with each completed DoD study.

a. Air Force-Sponsored Study (Cognitive Function in a Traumatic Brain Injury HBO₂ Randomized Trial): The first randomized controlled trial of HBO₂ was conducted as a single site study by the U.S. Air Force School of Aerospace Medicine at Wilford Hall Medical Center in San Antonio, Texas. It consisted of two groups with a total of 50 volunteer Service members with persistent PCS. Participants in one group breathed 2.4 ATA of medical grade oxygen (100 percent O₂, ppO₂ = 1796 mmHg) and the control group breathed 1.3 ATA of room air (21 percent O₂, ppO₂ = 207 mmHg). In this study, hyperbaric exposures were 90 minutes in length and scheduled for administration once per day, 5 days per week, over 8 weeks until a total of 30 sessions was reached. Using the Immediate Post-Concussion Assessment and Cognitive Testing (a measure of post-concussive sequelae), outcome measures focused on symptom relief and neurocognitive function. Participants were assessed at baseline, immediately post-completion of the experimental exposures, and six weeks thereafter.

b. Navy/Defense Advanced Research Projects Agency (DARPA)-Sponsored Study (HBO₂ Therapy for Post-Concussive Symptoms After mTBI: A Randomized, Double-Blinded, Sham-Controlled, Variable Dose, Prospective Trial): This study compared different doses of HBO₂ and was conducted by the Virginia Commonwealth University, the Naval Operational Medicine Institute, and the Hunter Holmes McGuire Veterans Administration (VA) Medical Center in Richmond, Virginia. This dose-ranging trial was performed in a single site in Pensacola, Florida. It consisted of three arms and randomized 60 volunteer Service members with PCS to breathe one of three different O₂ percentages (100 percent, 75 percent, or 10.5 percent O₂) while pressurized to 2.0 ATA (generating a ppO₂ equal to 1520, 1140, and 160 mmHg, respectively). Thus, the study's 75 percent O₂ breathing arm produced an oxygen exposure equivalent to breathing 100 percent O₂ at 1.5 ATA, whereas the 10.5 percent O₂ breathing arm produced an oxygen exposure equivalent to breathing the 21 percent O₂ present in regular room air. All hyperbaric exposures were 60 minutes in length and scheduled for administration once per day, 5 days per week, over 8 to 10 weeks until a total of 40 sessions were reached. Outcomes focused on symptom relief and neurocognitive function using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ). Beyond the baseline and immediate post-exposure assessments, this study additionally included a 3-month follow-up.

c. Army-Sponsored Hyperbaric Oxygen for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (HOPPS) Study (A Pilot Phase II Study of HOPPS): This study was a DoD multi-center Phase II trial conducted at Fort Gordon, Georgia; Fort Carson, Colorado; Camp Lejeune, North Carolina; and Camp Pendleton, California, with assistance of research staff from the Denver VA Medical Center, Colorado, and Latter Day Saints Hospital, Salt Lake City, Utah. This study consisted of three arms with a total of 72 volunteer Service members with

PCS. One arm breathed 100 percent O₂ at 1.5 ATA (ppO₂ = 1140 mmHg), one arm breathed room air (21 percent O₂) at 1.2 ATA (ppO₂ = 192 mmHg), and one arm underwent no chamber procedures, but continued to receive routine TBI care. This study's 60-minute hyperbaric exposures were scheduled for administration once per day, 5 days per week, over 10 weeks until a total of 40 sessions were reached. The outcomes focused on the evaluation of PCS symptoms and neurocognitive improvement, as well as methods to assess the components of the expected placebo effect. Outcomes were assessed at baseline and immediately after completion of the experimental exposure course. The RPQ served as this study's primary outcome measure, whereas the Neurobehavioral Symptom Inventory (NSI) was used as a secondary outcome measure.

d. Army-Sponsored BIMA Study (Brain Injury and Mechanisms of Action of HBO₂ for Persistent PCS after Mild Traumatic Brain Injury (BIMA)): This study was a DoD multi-center Phase II trial conducted at Joint Base Lewis-McChord, Washington; Fort Carson, Colorado; and Camp Lejeune, North Carolina, with the assistance of research staff from the Emmes Corporation, Rockville, Maryland; Lovelace Biomedical Environmental Research Institute, Albuquerque, New Mexico; and Intermountain Healthcare at the Latter Day Saints Hospital, Salt Lake City, Utah. This study consisted of two arms, with 71 subjects randomized to breathe either 100 percent O₂ at 1.5 ATA (ppO₂ = 1140 mmHg) or room air (21 percent O₂) at 1.2 ATA (ppO₂ = 192 mmHg). This study's 60-minute hyperbaric exposures were scheduled once per day, 5 days per week, and delivered over 12 weeks until a total of 40 sessions was reached. While the hyperbaric and sham exposure protocols in this study were identical to those used in HOPPS, the BIMA study included more volunteers per study arm. In addition, the BIMA was designed to assess a wider array of outcome measures, and incorporated a longer-term follow-up of subjects. More than 50 discrete outcomes were assessed across eight different domains, including PCS, sleep, and quality of life; neuropsychological performance; neurological, auditory, vestibular, visual and autonomic systems function; and neuroimaging. These outcome measures were assessed at baseline, 1 to 2 weeks after completion of experimental exposures, at 6 months after study enrollment, and, for the PCS and quality of life assessments, 12 months after study enrollment.

e. Army-Sponsored Louisiana State University (LSU) Study (HBO₂ Therapy Treatment of Chronic mTBI/Persistent Post-Concussion Syndrome): This study, currently underway at LSU, is a randomized prospective crossover-controlled clinical trial evaluating 100 percent O₂ breathing at 1.5 ATA (the hyperbaric exposure group, ppO₂ = 1140 mmHg) versus continuation of maintenance medication and counseling over the same period (the control group). The four sham-controlled studies described previously were double-blinded in design (i.e., both the investigators and the subjects were unaware of the intervention assignment). In contrast, neither the Principal Investigator nor the study participants in the LSU study are blinded to the study group assignments. A total of 59 volunteer Service members are expected to participate. The 60-minute hyperbaric exposures (with approximately 45 minutes of the exposure conducted at 1.5 ATA) are scheduled to be administered once per day, 5 days per week, over 8 weeks until a total of 40 sessions is reached. At the end of the 8-week exposure period, those individuals assigned to the control group are then "crossed over" to receive the same hyperbaric exposure as participants originally randomized to the hyperbaric exposure group.

4. RESULTS

The results of the four completed DoD-sponsored HBO₂ trials demonstrated that over a range of exposure times (60-90 minutes), pressures (1.2-2.4 ATA) and oxygen breathing conditions (90-1824 mmHg ppO₂), the hyperbaric and sham interventions were safe and well tolerated by the study participants. There were no significant adverse events related to the hyperbaric chamber exposures and adverse events that did occur were generally mild and reversible, consisting of minor ear and sinus barotrauma (squeezes). Participant follow-up for all studies exceeded 88 percent, but the range of participants completing all study exposures varied (49 percent in HOPPS, 8 percent in BIMA, 96 percent in the Air Force study, and 98 percent in the Navy/DARPA study).

In general, participants in the sham air and hyperbaric oxygen breathing groups experienced within-group improvement in their PCS symptoms relative to baseline, pre-exposure testing. With the exception of a relatively limited set of outcome measures in the BIMA study, none of the four completed DoD studies showed statistically significant benefits from HBO₂ therapy relative to the sham air exposures in the total study population. The specific findings of each study are reported below.

a. Air Force-Sponsored study: Evaluating the highest dose of HBO₂ among the DoD-sponsored trials, this study showed that no additional benefit was afforded to volunteers in the experimental treatment (HBO₂) group over the sham air control group. However, both arms did show statistically significant within-group improvements at the 6-week post-exposure assessments relative to baseline, which were considered by the investigators to be within the expected range for placebo or Hawthorne effects (i.e., 20-30 percent of subjects). Despite the relatively high chamber pressure and resultant dose of oxygen used, the exposure protocol was found to be safe and well-tolerated, with 96 percent of participants completing all planned study exposures. The results of this study were published in a series of three papers in the *Journal of Neurotrauma* in November 2012; the *Undersea and Hyperbaric Medicine Journal* in November-December 2012, and the *Undersea and Hyperbaric Medicine Journal* in July-August 2105 (Appendix A).

b. Navy/DARPA-Sponsored Study: This dose-ranging study showed no benefit in any of the treatment groups compared to sham controls on the RPQ (total or sub-scores), either immediately after treatment or 3 months after treatment. Within-group changes on the RPQ (total and sub-scores) demonstrated a non-significant trend toward improvement in the 2.0 ATA oxygen breathing group, but no change to slight worsening in the room air and 1.5 ATA oxygen equivalent breathing groups. Protocol adherence in this study was high, with 98 percent of volunteers completing all 40 scheduled chamber sessions. The results of this study were published in the *Neurorehabilitation and Neural Repair* in December 2013; *Journal of Head Trauma and Rehabilitation* in January-February 2014; and the *Annals of Neurology* in February 2014 (Appendix B).

c. Army-Sponsored HOPPS Study: This study showed no added benefit from HBO₂ treatment over the study's sham air control exposure. Statistically significant within-group improvements on the RPQ (total and sub-scores) and NSI were seen in participants in both

chamber exposure groups, but not in the routine TBI care group. Recording the lowest level of protocol adherence, 49 percent of this study's participants completed all 40 HBO₂ sessions. The study results were electronically published in the *Journal of the American Medical Association – Internal Medicine* on November 17, 2014, and in print on January 1, 2015 (Appendix C).

d. Army-Sponsored BIMA Study: The BIMA study was the most scientifically robust of the four completed DoD-sponsored mTBI trials, having the largest number of subjects per exposure group (35-36 in BIMA versus 18-25 in the other DoD studies), the greatest number and most diverse set of outcome measures, and the longest period of participant follow-up (extending out to 12 months post study enrollment). Overall, this study suggested a beneficial effect of hyperbaric oxygen over sham in reducing the symptoms of mTBI, as well as improvements in sleep, recall, and executive function measures, although most of the results were not statistically significant. The RPQ total score and the majority of the remaining self-reported symptom questionnaires, neurological function, and neuropsychological and quality of life outcome measures favored the HBO₂ group (39 of 43 measures); however, most of these improvements did not reach statistical significance. None of the improvements seen were sufficient to restore subjects to their expected pre-injury baseline. None of the improvements seen in the HBO₂ group were still significant beyond 6 to 12 months, indicating that the HBO₂ exposure effects on these self-reported symptom questionnaires and neuropsychological outcome measures were not lasting. Furthermore, while there was a shift toward normalization on a limited set of objective outcome measures (e.g., eye tracking movements), there was either no improvement or no relative between-group improvements on magnetic resonance imaging, computed tomography perfusion studies, neurological exam, most audiological and vestibular measures, or sleep measures that were not self-reported. 82 percent of study participants completed all 40 hyperbaric exposures, with 100 percent and 91 percent of HBO₂ and sham air group participants, respectively, available for the follow-up at the 12-month point. None of the study results have been published to date. A series of study manuscripts reporting the BIMA findings are under preparation for submission to peer-reviewed medical journals.

e. Army-Sponsored LSU Study: This study is ongoing, and, although study enrollment is nearing completion, the results are not available at this time. However, this study utilizes a crossover-control design in which neither the subjects nor the Principal Investigator are blinded to study allocation; therefore, it is unlikely that the outcomes of this study would significantly alter the conclusions of this report.

5. CONCLUSIONS

The completed DoD-sponsored HBO₂ studies showed that the hyperbaric and sham air exposure protocols used in the DoD studies were safe and well tolerated. With the exception of the BIMA study, none of the DoD studies showed statistically significant additional benefit from HBO₂ relative to the sham air exposures in the overall study population. Further, evidence from the BIMA study suggests that any improvement seen may be temporary, waning between 6 and 12 months after study completion. Accordingly, these DoD-sponsored mTBI studies support the conclusion that the estimated magnitude and duration of these effects in the general mTBI population are not sufficient to support use of HBO₂ as a treatment for PCS.

The results of these DoD studies differ from some anecdotal reports and case studies. However, those non-DoD investigators have not conducted any adequately controlled clinical trials capable of determining the effectiveness of HBO₂ for persistent PCS.

The DoD remains committed to researching, finding, and providing existing and new evidence-based treatments for mTBI for our injured Service members and their families. The DoD continues to evaluate new drug therapies, diagnostic biomarkers, prolonged exposure therapy, and cognitive behavioral therapy for mTBI.

6. POLICY CHANGES

Based on findings from the four completed DoD trials and the fact that neither the FDA nor professional hyperbaric medicine societies currently endorse the use of HBO₂ for mTBI, the DoD will not offer HBO₂ as an off-label or as an evidence-based therapy for mTBI. Accordingly, no policy changes relative to HBO₂ treatment of mTBI are indicated at this time.

7. APPENDICES: Lists of study publications

Appendix A: Air Force Study

- 1) The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. Wolf G, Cifu D, Baugh L, Carne W, Profenna L. *Journal of Neurotrauma*. 2012 Nov 20; 29(17):2606-12. doi:10.1089/neu.2012.2549. Epub 2012 Nov 9. PMID: 23031217
- 2) Hyperbaric side effects in a traumatic brain injury randomized clinical trial. Wolf EG, Prye J, Michaelson R, Brower G, Profenna L, Boneta O. *Undersea and Hyperbaric Medicine*. 2012 Nov-Dec;39(6):1075-82. PMID: 23342764
- 3) Cognitive function in a traumatic brain injury hyperbaric oxygen randomized trial. Wolf G, Baugh L, Shubert Kabban C, Richards M, Prye J. *Undersea and Hyperbaric Medicine*. 2015 Jul-Aug;42(6):313-332. PMID: 26403017

Appendix B: Navy Study

- 1) Randomized, sham-controlled, feasibility trial of hyperbaric oxygen for Service members with postconcussion syndrome: cognitive and psychomotor outcomes 1 week postintervention. Walker WC, Franke LM, Cifu DX, Hart BB. *Neurorehabilitation and Neural Repair*. 2013 Dec 26;28(5):420-432. [Epub ahead of print] PMID: 24370568
- 2) The effect of hyperbaric oxygen on persistent postconcussion symptoms. Cifu DX, Hart BB, West SL, Walker W, Carne W. J. *Head Trauma and Rehabilitation*. 2014 Jan-Feb;29(1):11-20. doi: 10.1097/HTR.0b013e3182a6aaf0. PMID: 24052094
- 3) Hyperbaric oxygen for blast-related postconcussion syndrome: three-month outcomes. Cifu DX, Walker WC, West SL, Hart BB, Franke LM, Sima A, Graham CW, Carne W. *Annals of Neurology*. 2014 Feb;75(2):277-86. doi: 10.1002/ana.24067. Epub 2014 Feb 20. PMID: 24255008.

Appendix C: Army HOPPS Study

- 1) Effects of hyperbaric oxygen on symptoms and quality of life among Service members with persistent postconcussion symptoms: a randomized clinical trial. Miller RS, Weaver LK, Bahraini N, Churchill S, Price RC, Skiba V, Caviness J, Mooney S, Hetzell B, Liu J, Deru K, Ricciardi R, Fracisco S, Close NC, Surrent GW, Bartos C, Ryan M, Brenner LA; HOPPS Trial Team. *JAMA Internal Medicine*. 2015 Jan 1; 175(1):43-52. doi: 10.1001/jamainternmed.2014.5479. PMID: 25401463

Appendix D: Army BIMA Study

- 1) A randomized trial of hyperbaric oxygen in U.S. military Service members with post-concussive symptoms. Weaver L, Wilson S, Lindblad A, Churchill S, Deru K, Price R, Williams C, Orrison W, Walker J, Meehan A, Mirow S, and the BIMA study team. Manuscript under preparation.