

## Invited Commentary

# The Ritual of Hyperbaric Oxygen and Lessons for the Treatment of Persistent Postconcussion Symptoms in Military Personnel

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**During the past decade**, unprecedented clinical and research resources have been directed toward addressing 2 conditions considered “silent” and “signature injuries” of the Iraq and



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Afghanistan wars, namely, posttraumatic stress disorder (PTSD) and concussion (mild traumatic brain

injury). This investment is increasingly paying dividends in knowledge and interventions that are changing the standards of clinical practice. Notable examples include emerging trauma-focused psychotherapies and the antihypertensive prazosin hydrochloride for PTSD.<sup>1</sup> However, along with these successes have also come seemingly promising interventions that in due course are shown to lack efficacy when tested in clinical trials such as the multicenter trial of risperidone augmentation for PTSD.<sup>1</sup>

This issue of *JAMA Internal Medicine* publishes results of a clinical trial that illuminates the challenges in designing effective interventions for silent war-related injuries.<sup>2</sup> While the sample size was modest, this unique well-designed 3-arm double-blind study of hyperbaric oxygen (HBO) treatment provides compelling results with broad implications. Seventy-two service members who experienced concussions (including at least 1 concussion during war-zone deployment) and were having persistent postconcussion symptoms ( $\geq 4$  months' duration) were randomized to receive 40 HBO treatments (100% oxygen at 1.5 atmospheres absolute for 60 minutes 5 days per week), a sham procedure (40 equivalent sessions involving slightly pressurized room air, sufficient to induce a feeling of inner ear pressure), or routine postconcussion care. Results showed that both the HBO and sham procedures were associated with significant improvements in postconcussion symptoms and secondary outcomes, including PTSD (which most participants had), depression, sleep quality, satisfaction with life, and physical, cognitive, and mental health functioning. However, there were no significant differences between HBO and the sham procedure, and change scores for all secondary outcomes favored sham.

Although this trial was technically a pilot investigation designed to produce data necessary for a pivotal study and will not likely end debate on this topic (given tenacious advocacy by HBO proponents<sup>3</sup>), these results are consistent with 2 other sham-controlled clinical trials among service members and veterans involving a range of HBO doses.<sup>2</sup> Given the outstanding methods, consistency in results, and lack of dose response across these studies, it is increasingly hard to argue that a phase 3 trial of HBO for the treatment of postconcussion symptoms (or PTSD) is warranted.

This conclusion is disappointing for service members and veterans experiencing war-related symptoms but offers important lessons and an opportunity to engage in renewed dialogue concerning the priorities for future interventions. This dialogue requires us to begin by acknowledging that no new treatments for persistent blast or impact-related postconcussion symptoms have been identified, despite the extensive investment to date. The evidence remains weak and inconsistent for both pharmacological (eg, stimulant or cholinergic augmentation) and nonpharmacological (eg, cognitive rehabilitation) interventions.<sup>4,5</sup> The only evidence-based treatment shown to be effective in attenuating persistent symptoms after concussion, based on clinical trials in civilian populations, is cognitive education to promote expectations of recovery.<sup>4,5</sup> However, despite this being emphasized as a cornerstone of treatment guidelines,<sup>4</sup> research is lacking to replicate or refine educational interventions in military or veteran populations. Furthermore, concerns have been raised that current screening approaches, combined with a specialty-driven structure of concussion care in the Veterans Health Administration and Department of Defense, may inadvertently promote negative, rather than positive, recovery expectations.<sup>5,6</sup>

This HBO clinical trial highlights a principal barrier to successful concussion-related interventions, namely, the fact that the condition of persistent postconcussion symptoms is such an elusive target for treatment that effective interventions will likely not be identified until this condition is reconceptualized.<sup>4,6</sup> Postconcussion symptoms typically involve headaches, fatigue, cognitive and memory problems, sleep disturbance, irritability, dizziness and balance problems, and others. However, these symptoms are ubiquitous in general medical practice, they are associated with numerous different conditions, and no validated clinical case definition exists, one of many reasons why this HBO pilot study was conducted. Multiple studies among military and veteran populations have shown that persistent cognitive and physical symptoms attributed to concussion in the postdeployment period are much more likely to be associated with conditions other than concussion, including PTSD, depression, grief, nonconcussive injuries, or associated comorbidities (eg, chronic pain and sleep dysfunction).<sup>5-7</sup> Underlying neuroendocrine and autonomic nervous system dysregulation likely mediates these multisymptom trauma-spectrum responses.<sup>1,5</sup>

Two-thirds of service members in this HBO study had a diagnosis of PTSD (based on structured clinical interviews), 44% were taking daily pain medication, and the mean depression scores were in the depressed range (with more than half tak-

ing an antidepressant), indicators of conditions likely to be stronger contributors to participants' nonspecific persistent symptoms than their concussions. The critical gap in clinical interventions will begin to get filled only when clinicians and researchers turn their attention to developing and validating interventions that respect the inherent nonspecific multitietiological nature of these symptoms (eg, through the use of coordinated step-care approaches based in primary care).<sup>4-8</sup>

The most remarkable lesson of this study was the difference in clinical outcomes between the 2 chamber procedures (HBO and sham) and routine postconcussion care. These differences, reflecting strong placebo effects on a par with those observed commonly in double-blind trials of pain and mental health treatments,<sup>8</sup> are particularly notable because this study was conducted in locations with robust postconcussion services that are anything but routine. These findings reinforce the argument that effective interventions do not yet exist within the present structure of care or that routine postconcussion interventions within the Department of Defense or Veterans Health Administration may even have iatrogenic effects that contribute to symptom persistence, the equivalent of a nocebo effect. The results also support the conclusion that these generalized multisymptom concerns can only be addressed through holistic clinical approaches. Rather than

specific interventions for a diagnosis that defies definition, the focus must shift to identifying the components of care that will maximize healing and functioning regardless of etiology.<sup>4-8</sup>

Although we may never know exactly why sham chamber treatment produced such effective placebo-related benefits in this study, what is clear is that this was a healing environment. Factors such as enhanced expectancy, conditioning, the authoritative context of care, and social reinforcement likely contributed,<sup>8</sup> as well as perhaps the prolonged break from the stresses of work. It is also conceivable that the daily ritual visitations during the 8 to 10 weeks of treatment fostered organic narrative processes between study participants and with their compassionate staff members, consistent with core components of effective PTSD and depression psychotherapy.<sup>1</sup>

In conclusion, this is an exemplary clinical trial that teaches us important lessons. Hyperbaric oxygen treatment does not work, but the ritual of the intervention does. The approach to postconcussion care among service members and veterans needs to be reconceptualized and priorities for clinical research focused accordingly. Additional research is needed to better understand the components of an optimal healing environment. This study invites us to rethink how we support service members and veterans in their recovery from complex war-related health concerns.

#### ARTICLE INFORMATION

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