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Letters to the Editor

A Phase I Study of Low-Pressure Hyperbaric Oxygen Therapy for Blast-Induced Post-Concussion Syndrome and Post-Traumatic Stress Disorder: A Neuropsychiatric Perspective

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Dear Editor,

We read with great interest the Phase I study of low-pressure hyperbaric oxygen therapy (HBOT) for blast-induced post-concussion syndrome (PCS) and post-traumatic stress disorder (PTSD) offered by Harch and associates in the journal's January issue (Harch et al., 2012). The study described therein illustrates the need for evidence-based treatments of the neuropsychiatric consequences of psychological and neurological trauma. However, the development of such treatments requires thoughtful application of the technologies they employ, and an appreciation for the vulnerability of individuals and families to the allure of promising but unproven treatments. Early in the development process, only cautious statements about the potential of such treatments to provide relief from complex and chronic conditions are appropriate. Remaining circumspect on these matters is essential when treatment entails more than minimal risks, assessments and treatments are costly, and their development is intertwined with commercial interests.

The medical, ethical, and public health consequences of prematurely deploying emerging technologies require careful consideration by medical providers, patients, and health care policy makers, especially when the evidence base for their use is under development (Adinoff and Devous, 2010; Wortzel et al., 2008). These issues are well articulated in a recent exchange of letters featured in the *American Journal of Psychiatry* (Adinoff and Devous, 2010; Amen, 2010), in which Adinoff and Devous offer readers a cautionary note and compelling charge: "Unfortunately, if previously led astray by unsupported claims, patients and their doctors may be less inclined to utilize scientifically proven approaches once these are shown in the peer-reviewed literature to be effective. It is therefore incumbent upon all of us to monitor and regulate our field" (Adinoff and Devous, 2010). It is in this spirit that we write this letter.

Paramount among our concerns is the authors' framing of their participants' clinical problems as sequelae of traumatic brain injury (TBI), and particularly "post-concussive syndrome," and their suggestion that reported clinical improvements are a consequence of HBOT-induced neuronal recovery. The World Health Organization Collaborating Centre Task Force on Mild Traumatic Brain Injury reviewed the literature on mild TBI (Carroll et al., 2004), and concluded unequivocally that this condition carries a favorable prognosis for the vast majority of individuals experiencing it, and that complete resolution of post-concussive symptoms is typical.

Most of the participants studied by Harch and colleagues (Harch et al., 2012) were individuals with remote mild TBI. Two participants experienced possible moderate TBI, and two others experienced complicated mild TBI. Inclusion of these four participants introduces unnecessary heterogeneity in terms of injury severity, and causes the group as a whole to be less representative of most persons with mild TBI. Their exclusion leaves a group whose persistent symptoms in the late post-injury period are consistent with atypical recovery from mild TBI, strongly suggesting that other neuropsychiatric conditions are contributors to the clinical presentations and functional limitations of the individuals comprising this study group (Carroll et al., 2004; Hoge et al., 2009; McCrea et al., 2009).

There are immediately apparent explanations other than neurotrauma for the symptoms and functional limitations experienced by the participants studied by Harch and associates (Harch et al., 2012). Based on the range of pre-HBOT

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PTSD Checklist-Military version (PCL-M) (Weathers et al., 1993; see note in references) scores reported in Table 6, all of these individuals had comorbid PTSD. The lowest PCL-M score was 48, the mean pre-treatment score was 67.4 ± 10, and the median score was 68, reflecting clinically significant levels of PTSD symptoms in the majority of these study participants (Blanchard et al., 1996; Mora et al., 2009; Weathers and Keane, 1991). The MacArthur Initiative on Depression & Primary Care defines remission of depression by a Patient Health Questionnaire-9 (PHQ-9) score <5 (MacArthur Initiative on Depression & Primary Care). By this definition, all of the participants studied by the Harch group (Harch, et al., 2012) also were clinically depressed pre-HBOT. On the Generalized Anxiety Disorder-7 (GAD-7) scale (Spitzer et al., 2006), scores of 5, 10, and 15, represent mild, moderate, and severe levels of generalized anxiety, respectively. In the Harch sample, the mean pre-HBOT GAD-7 score was 12.7 ± 5.8, with a median score of 14 and a range from 4–21. Accordingly, nearly all of these participants were experiencing clinically significant generalized anxiety. These participants also were receiving multiple psychotropic medications pre-HBOT. Based on the number of participants included in this study and the proportion taking agents from more than one medication class, psychotropic polypharmacy was the rule rather than the exception.

Simply put, the study population is most accurately described as one composed of individuals with comorbid PTSD, depression, generalized anxiety, and psychotropic polypharmacy, with a history of remote traumatic brain injuries that, for the most part, were of uncomplicated mild severity. Psychiatric comorbidities and polypharmacy may contribute to, or account entirely for, the elevated Rivermead Postconcussion Symptom Questionnaire (RPSQ) scores of these participants (Belanger et al., 2010; Benge et al., 2009). Unfortunately, Harch and colleagues offer neither a statistical analysis demonstrating the independence of RPSQ scores from PCL-M, PHQ-9, and/or GAD-7 scores, nor a report of the correlation between medication status and scores on any of these measures. Accordingly, the contribution of remote uncomplicated mild TBI to the clinical presentations of these participants at the time of study enrollment cannot be discerned from the data presented by Harch and colleagues (Harch et al., 2012).

The degree and clinical importance of the symptomatic changes experienced by participants in this study also are doubtful. Harch and colleagues (Harch et al., 2012) elected to compare mean PCL-M, PHQ-9, GAD-7, and RPCS scores pre- and post-HBOT rather than *a priori* defining "treatment response" based on a specific decrease in score on these measures that is commonly accepted as indicating a clinically meaningful change. Based on the results presented in Table 3, many of the participants in their study continued to experience clinically important levels of PTSD, depression, and generalized anxiety, despite treatment with HBOT. Their data (i.e., "percent back to normal") also clearly demonstrate that most of these participants continued to experience a broad range of clinically important cognitive, physical, and emotional symptoms despite HBOT.

The extent to which HBOT contributed to the relatively modest observed changes in PTSD and depressive and generalized anxiety symptoms also requires re-consideration. The conduct of an uncontrolled study in which participants with multiple comorbid psychiatric illnesses receive psychotropic polypharmacy, undergo extensive pre- and post-treatment clinical and neuroimaging assessments, and are provided 40 unblinded HBOT experiences, creates a high likelihood of placebo response. Harch and co-workers (Harch et al., 2012) are dismissive of the possible contribution of expectation bias (i.e., placebo effect) created by their uncontrolled intervention, arguing that "placebo effects are overestimated in observational studies such as ours." The design of their study protocol and its participants cast doubt on this claim.

Their participants experienced frequent interactions with study personnel, at least 40, given the number of HBOT administrations. It would be difficult to accept an argument suggesting that their study staff failed to provide basic support, education regarding the proposed study intervention, and therapeutic optimism, all of which contribute to placebo response (Sinyor et al., 2010). The notion that response expectations are not engendered by the impressive technology used during HBOT also appears false on its face (see http://www.hbot.com/). Even if HBOT engenders no more treatment response expectations than ingestion of study drug or engagement in psychotherapy, placebo responses among clinical trial participants with depression, anxiety disorders, and PTSD are well established (Nelson and Devanand, 2011; Sinyor et al., 2010; Stein et al., 2006a,2006b). Additionally, failure to include active comparators increases the rate of placebo response among persons with depression participating in clinical trials (Sinyor et al., 2010; Stein et al., 2006a). The authors also suggest that their single-photon emission computed tomography (SPECT) results argue against placebo effect, and that the diffuse perfusion changes they observed differ from the focal changes typically associated with placebo response. However, review of the citations (Beauregard, 2009; Jarcho et al., 2009) used to support this claim reveals that the neuroimaging correlates of placebo effects are not well established. In fact, Jarcho and associates (Jarcho et al., 2009) state explicitly that "…most neuroimaging studies of placebo effects have been limited to healthy individuals receiving experimentally-induced noxious stimuli. Because of this limitation, it is unclear whether findings will generalize to clinical settings."

The dramatic neuropsychological improvements reported by Harch and associates (Harch et al., 2012) also are concerning. The extant neuropsychological literature shows no decrement in intellectual functioning following mild TBI (Belanger et al., 2005; Belanger and Vanderploeg, 2005). Therefore, a mean 14.8-point Full Scale IQ improvement is hard to interpret. A possible explanation is that poor performance effort was a major factor adversely impacting baseline IQ assessments. Similarly, the observed improvements in working memory, delayed memory, and executive function, are far larger than any cognitive decrements that may exist in these areas in the late period following mild TBI. Several meta-analytic studies of persons with mild TBI establish expectations for return to baseline cognitive performance (i.e., typical recovery) within 7 days following sports concussions (Belanger and Vanderploeg, 2005), or within 30 days following non-sports concussions (Belanger et al., 2005). The medical literature suggests that most individuals with mild TBI do not experience long-term cognitive impairments (Dikmen et al., 2009), and even those with a history of multiple mild traumatic brain injuries do not typically experience cognitive

impairments of this magnitude (Belanger et al., 2010). The authors acknowledge that practice effects may have contributed to the cognitive improvements observed, but regard that possibility as unlikely. However, they never address the far more concerning issue of performance validity. Interestingly, although they report administering the Green Word Memory Test to assess patient performance effort at baseline, those results are never presented.

The authors note that post-HBOT clinical changes were mirrored by "a reciprocal reduction or elimination of psychoactive and narcotic prescription medication usage in 64% of those participants for whom they were prescribed." In fact, pre-HBOT medications used by their participants included: SSRIs/atypical antipsychotics/atypical antidepressants (9 participants); anxiolytics/hypnotics (8 participants); anticonvulsants (5 participants); anti-migraine medication (4 participants); narcotics (3 participants); vasodilators (2 participants); muscle relaxants (2 participants); and antihistamines/antiemetics, cholinesterase inhibitors, and stimulants (1 subject each). Nine of the 15 participants (60%) completing HBOT were taking more than one medication; based on these numbers, these nine participants were taking several medications. As noted earlier, the contribution of polypharmacy to the presenting symptoms of these individuals may have been substantial. This possibility is unaddressed by the Harch group (Harch et al., 2012). The possible influence of both pre-treatment polypharmacy and post-HBOT reductions in medication use on study assessments—including self-reported symptoms, neuropsychological testing, and/or SPECT imaging—also is entirely unaddressed by these authors.

In light of all of these issues, the effects of HBOT on the clinical problems and SPECT imaging profiles observed by Harch and colleagues (Harch et al., 2012) are uncertain. Even less certain is the relevance of HBOT to mild TBI and "post-concussive" symptoms in this population: one in which TBI types and severities are heterogeneous; pre-morbid psychiatric and substance use disorders are not reported; persistent symptoms are post-concussive only as a function of occurring after – not necessarily because of – mild TBI; and clinical presentations at the time of study enrollment are strongly influenced by multiple psychiatric comorbidities and psychotropic polypharmacy. The authors' suggestion that HBOT was usually well tolerated is not unreasonable. However, their claims of efficacy and the use of SPECT to support them are premature and not supported by their data. Accordingly, their observations and interpretations require reconsideration.

Author Disclosure Statement

No competing financial interests exist. The opinions offered in this work do not necessarily reflect those of the VISN-19 MIRECC or the Department of Veterans Affairs.

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