Improvements in Gulf War Illness Symptoms After Near-Infrared Transcranial and Intranasal Photobiomodulation: Two Case Reports

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ABSTRACT At least one-fourth of US veterans who served in the 1990–1991 Gulf War (GW) are affected by the chronic symptomatic illness known as Gulf War illness (GWI). This condition typically includes some combination of fatigue, headaches, cognitive dysfunction, musculoskeletal pain, and respiratory, gastrointestinal and dermatologic complaints. To date, effective treatments for GWI have been elusive. Photobiomodulation (PBM) describes the non-pharmacological, non-thermal use of light to stimulate, heal, and protect tissue that has either been injured, is degenerating, or else is at risk of dying. Significant benefits have been reported following application of transcranial PBM to humans with acute stoke, traumatic brain injury (TBI), and dementia. This report describes the first documentation of improved GWI symptoms in two GW veterans following 12 weeks of PBM treatments.

INTRODUCTION

Epidemiological studies have consistently described a profile of chronic symptoms that afflict veterans of the 1991 Gulf War (GW) from the US and other countries at significantly higher rates than other veteran groups.[1] This condition, commonly known as Gulf War illness (GWI), is estimated to affect one fourth of the nearly 700,000 US GW veterans.[2,3] Characterized by multiple concurrent symptoms that include some combination of persistent headaches, cognitive difficulties, joint and musculoskeletal pain, fatigue, gastrointestinal problems, and other chronic abnormalities, GWI has not been accounted for by medical or psychiatric conditions routinely diagnosed in clinical practice. Longitudinal studies indicate that few veterans with GWI have recovered or improved substantially improved over time[4,5] and, unfortunately, effective treatments for GWI are lacking.[6] Although the condition was initially dubbed "Gulf War Syndrome," the US Department of Veterans Affairs (VA) prefers not to use this term when referring to medically unexplained symptoms reported by GW veterans because symptoms vary widely.[7]

Research on GWI has relied on a couple of different definitions of the disorder, including chronic multisymptom illness (CMI[8]) and the Kansas GWI case definition.[2] CMI has been used the most commonly in epidemiologic research to date.[9] To meet criteria for CMI, GW veterans must report one or more symptoms that have been going on for at least 6 months in two of three categories (i.e., fatigue, pain, and mood-cognitive problems, see Table I). CMI can be further categorized as "severe" if the veteran rates each defining symptom as severe or "mild-moderate" if the veteran rates each defining symptom as mild or moderate. This case definition has been recommended for clinical use by an Institute of Medicine panel on GWI case definitions.[10] To meet criteria for Kansas GWI, GW veterans must report moderately severe or multiple chronic symptoms in at least three of six categories[2] (i.e., fatigue/sleep problems, pain, neurological/cognitive/mood problems, respiratory problems, gastrointestinal problems, or skin problems, see Table II). Additionally, veterans who have severe psychiatric disorders or other medical conditions that might predict similar symptoms are excluded as Kansas GWI cases. The Institute of Medicine report on GWI case definitions recommended this definition be used for research purposes.[10]

Photobiomodulation (PBM) is a non-pharmacological treatment that uses light, most commonly in the red or near-infrared (NIR) spectrum, to stimulate, heal, and protect tissue that has either been injured, is degenerating, or is at risk of dying.[11] PBM was initially investigated for stimulating wound healing and reducing pain and inflammation in various orthopedic conditions such as tendonitis, neck pain, and carpal tunnel syndrome.[12] The first in vivo evidence of the neurotherapeutic effects of PBM were achieved in the rabbit embolic stroke model to test its ability to prevent damage or repair damage to the brain occurring after a stroke.[13] The neuroprotective effects of PBM have since been demonstrated in diverse neurological conditions such as traumatic brain injury (TBI),[14–16] ischemic stroke,[17–19] dementia,[20] and psychological disorders such as depression and anxiety.[21,22] This report describes two veterans with GWI who experienced symptom reduction following 12 weeks of treatments with a commercially available PBM device.

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doi: 10.1093/milmed/usz037

TABLE I. CMI Symptoms[a]

	GWVI		GWV2	
	Baseline	Week 12	Baseline	Week 12
Fatigue domain				
Fatigue	1	0	3	1
Feeling unwell after physical exercise or exertion	1	0	2	1
Pain domain				
Pain in joints	1	1	3	2
Pain in muscles	0	0	3	0
Mood-cognitive domain				
Feeling down or depressed	1	0	1	1
Feeling irritable or having angry outbursts	1	1	3	0
Difficulty concentrating	1	1	1	0
Difficulty remembering recent information	1	1	2	0
Feeling worried/tense/anxious	1	0	2	0
Trouble finding words when speaking	1	1	2	0
Problems getting to sleep or staying asleep	1	0	3	0
Total Fatigue Domain Score	2	0	5	2
Total Pain Domain Score	1	1	6	2
Total Mood-Cognitive Domain score	7	4	14	1

[a]0 = no symptom, 1 = mild symptom, 2 = moderate symptom, 3 = severe symptom

METHODS

Table III summarizes the demographic, clinical, and medical characteristics of the two GW veteran participants. Both veterans had participated in a VA-funded study examining the effects of service in the Gulf War on brain function and brain structure. As part of that study, they underwent clinical interviews to assess for psychiatric comorbidities (e.g., post-traumatic stress disorder, major depressive disorder, history of alcohol abuse or dependence, history of substance abuse or dependence) and history of TBI. The veterans were asked to participate in the pilot study because they met the CMI case definition.[8]

After obtaining written informed consent from the veterans, baseline questionnaires (i.e., the Kansas Gulf War Military History and Health Questionnaire,[2] the Insomnia Severity Index [ISI],[23] and the Brief Pain Inventory [BPI][24]) were administered to obtain information about nature and severity of the veterans' current symptoms. After completing the questionnaires, the veterans were given Vielight Neuro Alpha PBM devices (see Fig. 1) to use for duration of the pilot study. After 12 weeks, the veterans returned to complete the same questionnaires about their symptoms.

STUDY OUTCOME MEASURES

The study outcome measures, assessed by self-report questionnaires at baseline and after 12 weeks of PBM treatments, included Kansas GWI[2] symptoms (see Table II), CMI symptoms[8] (see Table III); both were assessed with the Kansas Gulf War Military History and Health Questionnaire[2]). A GWI symptom severity index was derived by summing scores of the six Kansas GWI domains, which yielded a score that ranged from 0 to 90. Other outcome measures included pain symptoms (assessed with the BPI[24]) and sleep difficulties/insomnia severity (assessed with the ISI[23]).

PBM DEVICE DESCRIPTION AND TREATMENT PROTOCOL

The Vielight Neuro Alpha device (see Fig. 1), which is commercially available for about $1,700, was used in the study. According to the Food and Drug Administration document, "General Wellness: Policy for Low Risk Devices," released on July 29, 2016, the Vielight Neuro Alpha device would be considered a non-regulated, "low risk general wellness product."

The PBM device has five light emitting diodes (LEDs) that emit 810 nm NIR light. The transcranial diodes on the skull are held in position by two lateral stainless-steel bands. The intranasal diode fits inside the nostril and is held in place with a plastic clip. The power density of the transcranial LED diodes are: 100 mW/cm^2 for the 3 posterior LEDs, 75 mW/cm^2 for anterior LED, and 25 mW/cm^2 for the intranasal LED. All diodes are pulsed at a synchronized rate of 10 Hz, 50% duty cycle. The device is powered by rechargeable NiMH batteries and shuts off automatically after 20 min of treatment time. No significant heat is generated.

TREATMENT PROTOCOL

The veterans were instructed to use the PBM device every other day, preferably at the same time each day. To encourage adherence to the home PBM treatment regimen, the veterans were asked to record each treatment in a home treatment journal. The veterans were monitored for safety and any adverse events through twice monthly telephone calls.

TABLE II. Kansas GWI Symptoms[a]

	GWVI		GWV2*	
	Baseline	Week 12	Baseline	Week 12
Fatigue domain				
Fatigue	1	0	3	1
Feeling unwell after physical exercise or exertion	1	0	2	1
Problems getting to sleep or staying asleep	1	0	3	0
Unrefreshing sleep	1	1	3	1
Pain domain				
Pain in joints	1	1	3	2
Pain in muscles	0	0	3	0
Body pain, hurt all over	0	0	3	1
Neurological/cognitive/mood (NMC) domain				
Headaches	1	1	3	2
Feeling dizzy, lightheaded, faint	1	0	2	0
Eyes sensitive to light	0	0	3	0
Blurred or double vision	1	0	3	0
Numbness or tingling in extremities	2	0	1	0
Tremors or shaking	0	0	1	1
Low tolerance for heat/cold	0	0	2	1
Night sweats	0	0	3	1
Physical or mental symptoms to certain smells/chemicals	0	0	3	0
Difficulty concentrating	1	1	1	0
Difficulty remembering recent information	1	1	2	0
Trouble finding words when speaking	1	1	2	0
Feeling down or depressed	1	0	1	1
Feeling irritable or having angry outbursts	1	1	3	0
Skin domain				
Skin rashes	0	0	2	2
Other skin problems	0	0	1	0
Gastrointestinal domain				
Diarrhea	0	0	1	0
Nausea or upset stomach	0	0	1	0
Abdominal pain or cramping	1	0	1	0
Respiratory domain				
Difficulty breathing or catching breath	1	0	1	0
Frequent coughing in absence of cold	1	0	2	0
Wheezing in chest	0	0	1	1
Domain scores				
Fatigue	4	1	11	3
Pain	1	1	9	3
NMC	10	5	30	6
Skin	0	0	3	2
Gastrointestinal	1	0	3	0
Respiratory	2	0	4	1
GWI Symptom Severity Index[b]	18	8	60	12
No. symptom domains with scores ≥2	4	2	6	5

*GWV2 did not meet the Kansas GWI case definition at baseline because of two exclusionary conditions (cancer and melanoma).
[a]0 = no symptom, 1 = mild symptom, 2 = moderate symptom, 3 = severe symptom.
[b]Derived by summing all 6 symptom domain scores.

The home treatment journals were reviewed at the Week 12 in-person assessment.

RESULTS

GWV1

At baseline, GWV1 was classified as a Kansas GWI case[2] (i.e., he had no exclusionary conditions and 4 Kansas GWI symptom domain scores that were ≥2; see Table II). After 12 weeks of PBM treatments, GWV1 no longer met the criteria to be considered a Kansas GWI case. Although GWV1 remained a mild-moderate CMI case at Week 12, his mood-cognitive domain score, pain, sleep, and fatigue symptoms all improved (see Tables III and IV).

GWV2

GWV2 did not meet the Kansas GWI case definition at baseline because he had two exclusionary conditions (i.e., cancer

TABLE III. Demographic, Military, Health Characteristics of Two GW Veteran (GWV) Participants

	GWV1	GWV2
Age	66	56
Ethnicity	Asian	Caucasian
Handedness	Right	Right
Education level	Some college or vocational school	Some college or vocational school
Marital status	Married	Married
Military characteristics during GW		
Branch of service	Navy	Army
Rank	Enlisted	Enlisted
Time deployed in Gulf Region	July, 1990–March, 1991	March, 1990–May, 1991
Deployment location(s)	Dubai and Jebel Ali (was primarily at sea during deployment)	Saudi Arabia (Northern, Central, and Eastern regions), Kuwait, Iraq
Job during GW	Machinist	Medic
Mental Health Characteristics		
Trauma exposure	Yes	Yes
Lifetime CAPS[a]	17	102
Current CAPS[a]	0	13
Current PTSD	No	No
Lifetime history of MDD	Yes	Yes
Current MDD	No	No
Beck Depression Inventory[a]	4	3
History of alcohol abuse/ dependence	Yes	Yes
History of substance abuse/ dependence	No	No
History of TBI[b]	Improbable	Mild
Current Smoker	Yes	No (no but chews tobacco)
Smoked during GW	Yes	No
Current medical conditions	High blood pressure high cholesterol type II diabetes, arthritis/chronic joint pain back pain	High cholesterol sarcoidosis of lung type II diabetes arthritis/chronic joint pain back pain
Current medications	Lisinopril Avandamet Simvastatin Bupripon	Metformin Ezetimibe Methotrexate Infixmab Alendronate Omeprazole Albueterol

GW: Gulf War; CAPS: Clinician Administered PTSD Scale; PTSD: Posttraumatic Stress Disorder; MDD: Major Depressive Disorder; TBI: Traumatic Brain Injury.

[a]Higher scores = more severe symptoms.

[b]Assessed with the Ohio State University TBI Identification Method (OSU TBI-ID) Short Form.[58]

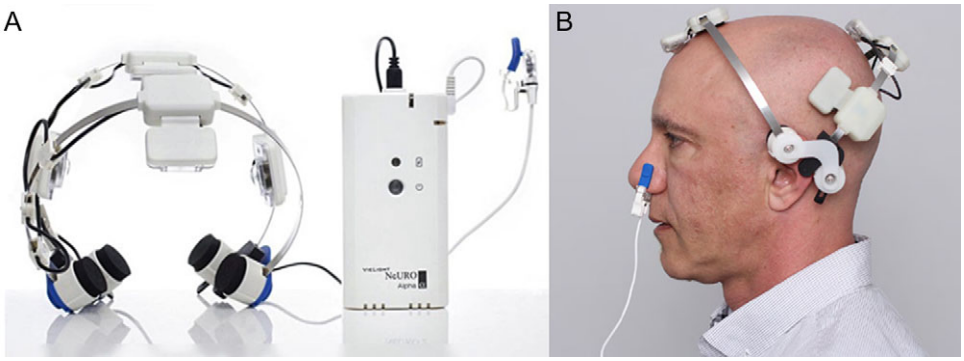

FIGURE 1. (A) Picture of Vielight Neuro Alpha device and (B) corresponding positioning of the transcranial and intranasal LEDs. Figure courtesy of Vielight Inc.

TABLE IV. Pain and Sleep/Insomnia Symptoms

	GWVI		GWV2	
	Baseline	Week 12	Baseline	Week 12
Brief Pain Inventory score	70	28	55	45
Insomnia Severity Index	11	5	15	3

Higher scores on both measures indicate worse/more severe symptoms.

and melanoma). However, he was classified as a severe CMI case. After 12 weeks of PBM, GWV2 was re-classified as a mild-moderate CMI case because he rated most symptoms as "mild" or "moderate." At Week 12, his fatigue, pain, and mood-cognitive, pain and sleep symptoms all improved (see Tables III and IV).

Both veterans tolerated the PBM intervention well. There were no reports of any adverse events.

DISCUSSION

To our knowledge, these two cases represent the first documentation of GWI symptom improvements after PBM treatments. GWV1, who met both the Kansas GWI[2] and CMI[8] case definitions at baseline, no longer had enough symptoms to be classified as a Kansas GWI case at Week 12. GWV2 was not classified as Kansas GWI[2] case because of exclusionary conditions. Nevertheless, he had GWI symptoms at baseline, which improved after 12 weeks of PBM treatments. GWV2's symptoms, quantified by the GWI Symptom Severity index, improved 48 points (from 60–12). This symptom reduction was enough to re-classify GWV2, who had been a severe CMI case at baseline, as a mild-moderate CMI case at Week 12.

Insomnia and sleep disturbances are common in veterans with GWI. Therefore, it is significant that this non-pharmacological intervention reduced the veterans' symptoms of insomnia. There was a 6-point reduction in GWV1's ISI and a 12-point reduction in GWV2's ISI. A 6-point reduction in the ISI has been considered clinically meaningful improvement in primary insomnia.[25]

Pain is another common symptom of GWI. In this study, 12 weeks of PBM reduced pain symptoms in both veterans. There was a 42-point reduction in GWV1's BPI and a 10-point reduction in GWV2's BPI. A two-point reduction in the BPI was deemed to be the minimum clinically important difference (MCID) for several pain measures obtained from the BPI in a study that pooled data across 4 randomized, double-blind, placebo-controlled 12-week treatment studies of a pharmacological (duloxetine) treatment for fibromyalgia.[26] The reductions in BPI in the present study were considerably larger than the 2-point MCID, which corresponded to a 30–35% improvement from baseline to end point.[26]

Although the etiology of GWI has not yet been fully elucidated, there is increasing evidence implicating exposure to multiple potentially hazardous chemicals in the Gulf War theater: For example, veterans who reported using pesticides and pyridostigmine bromide (PB) pills, which was administered prophylactically as a protective measure against possible nerve agent exposure, during deployment have significantly higher rates of GWI than veterans who did not use these compounds in theater.[27] In addition to using PB and pesticides, some GW veterans were also exposed to low-levels of chemical nerve agents, such as sarin and cyclosarin,[6] during their time in the GW. Nerve agents, PB, and many of the pesticides used during the GW fall into a class of chemicals known as acetylcholinesterase inhibitors.

There is suggestive evidence that acetylcholinesterase inhibitors cause toxicity and lethality through oxidative stress and mitochondrial dysfunction[28] more than through its interference with breakdown of the neurotransmitter acetylcholine. In this respect, it is noteworthy that mitochondrial dysfunction has been suggested to be a potential mechanism of GWI that would explain not only the multiplicity and variability of GWI symptoms, but also the variable latency to onset of GWI symptoms and the objective markers linked to GWI.[29,30] Results from a recently completed clinical trial provide further support for the role of mitochondrial dysfunction in GWI: Golomb et al.[31] reported that self-rated general health in male veterans with GWI improved after 3.5 months of using 100 mg of coenzyme Q10 (coQ10), an anti-oxidant that improves symptoms associated with mitochondrial dysfunction.[32]

The best studied mechanism of PBM centers around cytochrome c oxidase (CCO), which is the last unit of the mitochondrial respiratory chain responsible for the final reduction of oxygen to water using the electrons generated from glucose metabolism. Research suggests that CCO activity may be inhibited by nitric oxide (NO), particularly in hypoxic or damaged cells.[11,33] This inhibitory NO may be dissociated by photons of light absorbed by CCO, which have two heme and two copper centers that act as photoacceptors.[34–36] The dissociation of NO from CCO increases mitochondrial membrane potential, causing more oxygen to be consumed, more glucose metabolism, and more ATP production by the mitochondria.[11,33,37] This is supported by reports that PBM increases ATP content and decreases oxidative stress and NO production.[38]

There is also suggestive evidence of a brief increase in reactive oxygen species (ROS) produced in the mitochondria when photons of light are absorbed during PBM. This brief burst of ROS may, in turn, trigger some mitochondrial signaling pathways leading to cytoprotective, anti-oxidant and anti-apoptotic effects in the cells.[39] There have been reports that PBM decreases apoptosis after rotenone- and MPP^+-induced toxicity.[38] The NO that is released by photodissociation acts as a vasodilator as well as a dilator of lymphatic flow. Moreover, NO is also a potent signaling molecule and can activate a number of beneficial cellular pathways.[40]

In this study, NIR light was primarily delivered transcranially, through four LED clusters on the head. Research with cadavers has shown that NIR light can measurably penetrate

the scalp, skull, and meninges[41] to a depth of approximately 40 mm in the brain.[42] This is why PBM can be delivered transcranially to target the brain parenchyma in humans. The reduction in GWI symptoms noted in these two GWI cases may relate to reports that PBM therapy increases cerebral blood flow,[21,43,44] augments brain energy metabolism,[45] and increases antioxidant defenses.[46] Moreover, PBM's ability to promote neuronal protection and survival is mediated through modulation of anti-apoptotic and pro-apoptotic mediators[47,48] and inflammatory signaling molecules[49,50] as well as the stimulation of neurotrophic factors.[51–53] Besides these therapeutic effects at the molecular level, there is also considerable evidence of changes occurring at the behavioral level such as cognitive enhancement, antidepressant effects, and improved sleep.[21,54–56]

CONCLUSIONS

Results of these two case reports suggest that PBM therapy may be safely used to help alleviate many GWI symptoms. PBM was well tolerated by both veterans and there were no adverse effects. However, the treatments will likely need to be continued on a regular basis based on previous studies that suggest the effects of PBM are not maintained.[20,57] This points to the importance of having PBM devices that are amenable to home use for treating GWI. These promising, preliminary results suggest that future, larger-scale, controlled trials of home PBM for GWI are warranted.

FUNDING

VA grant No. 1I01CX000798 entitled "Longitudinal Assessment of Gulf War Veterans with Suspected Sarin Exposure."

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