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# Gulf War Illness: A Systematic Review of Therapeutic Interventions and Management Strategies

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April 2020

**Prepared for:**

Department of Veterans Affairs  
Veterans Health Administration  
Health Services Research & Development Service  
Washington, DC 20420

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**U.S. Department of Veterans Affairs**

Veterans Health Administration  
Health Services Research & Development Service



## PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of 4 ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the [program website](#).

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at [Nicole.Floyd@va.gov](mailto:Nicole.Floyd@va.gov).

**Recommended citation:** Freeman M, Nugent SM, Ayers CK, Winchell KA, Press A, O’Neil ME, Kansagara D. Gulf War Illness – A Systematic Review of Therapeutic Interventions and Management Strategies. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #05-225; 2020. Available at: <https://www.hsrd.research.va.gov/publications/esp/reports.cfm>.

This report is based on research conducted by the Evidence Synthesis Program (ESP) Center located at the located at the Portland VA Health Care System, Portland, OR, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

## ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Karen Block, PhD, Director of Gulf War Research in the Veterans Affairs (VA) Office of Research and Development (ORD) Gulf War Research Program, for the purpose of informing the planning for a state-of-the-art meeting on Gulf War Research and providing guidance for ORD funding priorities in Gulf War research. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the Technical Expert Panel (TEP).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors gratefully acknowledge Robin Paynter, MLIS, and the following individuals for their contributions to this project:

### Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend TEP participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

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### Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

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## Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

## ABSTRACT

**Aim:** We conducted a systematic review of therapeutic interventions for Gulf War Illness (GWI) to evaluate effectiveness and harms and identify potentially promising treatments.

**Methods:** We searched electronic databases, trial registries, and reference lists through September 2019 for randomized and non-randomized controlled trials and cohort studies directly comparing interventions for Veterans with GWI to each other, placebo, or usual care. We abstracted data on study design, demographics, interventions, and outcomes. Two reviewers independently assessed studies for inclusion, quality, and strength of evidence using pre-specified criteria. We resolved discordant ratings by discussion and consensus.

**Results:** We identified 12 RCTs, each of which examined a different intervention for GWI. We found moderate-strength evidence that cognitive behavioral therapy (CBT) and exercise, separately and in combination, were associated with improvements in several GWI symptom domains. There was low-strength evidence of benefit from 2 mindfulness-based interventions and Continuous Positive Airway Pressure (CPAP). Mindfulness-based stress reduction improved pain, cognitive functioning, fatigue, depression, and posttraumatic stress disorder (PTSD), while mind-body bridging improved fatigue, depression, PTSD, and sleep, although pain and other outcomes did not improve. CPAP improved overall physical health, pain, cognitive functioning, fatigue, mental health, and sleep quality in a small study of Veterans with sleep-disordered breathing and GWI. We found moderate-strength evidence that doxycycline is ineffective for GWI in mycoplasma DNA-positive Veterans and increases the risk of adverse effects compared with placebo. We also found 33 ongoing, single-arm pilot, or unpublished studies examining a variety of interventions.

**Conclusion:** There is moderate-strength evidence of benefit from CBT and exercise, and low-strength evidence of benefit from 2 distinct mindfulness-based interventions as well as CPAP. Doxycycline was ineffective and associated with harms (moderate-strength evidence). Emerging evidence examines a wide array of treatments. Larger, more rigorous studies are needed to reproduce and characterize positive findings.

## EXECUTIVE SUMMARY

### AIM

We conducted a systematic review to evaluate the effectiveness and harms associated with therapeutic interventions for Gulf War Illness (GWI) and its related symptoms. This review helps to identify treatments that warrant further inquiry, as well as treatments with a moderate base of evidence showing lack of effect and potential for harm.

### METHODS

We searched electronic databases, clinical trial registries, and reference lists through September 2019 for randomized and non-randomized controlled trials (RCT/nRCT) and cohort studies directly comparing interventions for Veterans with GWI to each other, placebo, or usual care. We excluded studies that compared interventions in Veterans without GWI to those with GWI, unless there was a separate analysis of the comparison in only those with GWI. We also excluded non-comparative studies except when summarizing emerging research. We abstracted data on study design, demographics, interventions, and outcomes. Two reviewers independently assessed studies' full text for inclusion, quality (risk of bias [ROB]), and strength of evidence (SOE) using published criteria and resolved discordant ratings by discussion and consensus.

### RESULTS

We identified and synthesized the evidence from 12 RCTs, each of which examined a different intervention for GWI (Figure i). We found several promising – but not definitive – treatments for various symptoms associated with GWI. We found moderate-strength evidence that cognitive behavioral therapy (CBT), exercise, and the combination of the 2 were associated with improvements in several GWI symptom domains. We found low-strength evidence that the following interventions improved 1 or more outcomes in patients with GWI:

- Mindfulness-based stress reduction (MBSR) improved\* pain, cognitive functioning, fatigue, depression, and posttraumatic stress disorder (PTSD).
- Mind-body bridging (MBB) – another type of mindfulness intervention – improved\* fatigue, depression, PTSD, and sleep, though it did not improve overall physical or mental health, pain, or cognitive functioning.
- Continuous Positive Airway Pressure (CPAP) improved\* overall physical health, pain, cognitive functioning, fatigue, mental health, and sleep quality in a small study of Veterans with sleep-disordered breathing and GWI.

We found moderate-strength evidence that doxycycline is ineffective for GWI in mycoplasma DNA-positive Veterans and increases the risk of adverse effects compared with placebo. We found no effects of treatment with mifepristone, naltrexone, or rifaximin on GWI-associated symptoms, and some indications of benefit with carnosine, Coenzyme Q<sub>10</sub> (CoQ10), acupuncture, and detoxification, though the SOE for these findings was insufficient to draw

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\*Specifics on improvement for these outcomes are defined in the subsequent full report

conclusions due to methodical limitations of the studies. No studies examined the effects of interventions on respiratory or dermatologic outcomes.

Most of this evidence base consists of small studies each examining a different intervention, and the findings described are likely to change as more research is conducted. We identified 31 ongoing or unpublished studies, 2 published single-arm studies, and 2 studies that were terminated prior to completion. Few of these ongoing studies examine an intervention that has previously been studied: 2 of cognitive behavioral approaches, 1 of MBSR, and 1 with an acupuncture component. Aside from 2 ongoing studies examining forms of transcranial direct current stimulation (tDCS), and 3 examining repetitive transcranial magnetic stimulation (rTMS), no 2 ongoing studies address the same intervention, and the interventions examined by the remaining 22 studies vary widely.

**Figure i. Summary of findings**

Treatment <i>Subpopulation if applicable</i>	Outcome domain										
	Physical health overall	Pain	Cognitive	Fatigue	Mental health overall	Depression	Global outcomes (function, QoL)	PTSD symptoms	Sleep	GI symptoms	Adverse events
<b>Medications vs placebo</b>											
Doxycycline <sup>1</sup> <i>Positive mycoplasma</i>	□□	□□	□□	□□	□□	---	---	---	---	---	□□
Mifepristone <sup>2</sup>	∅	---	∅	∅	∅	∅	---	∅	---	---	∅
Naltrexone <sup>3</sup>	∅	---	∅	---	---	---	---	---	---	---	∅
Rifaximin <sup>4</sup> <i>IBS (Rome III)</i>	---	---	---	---	---	---	∅	---	---	∅	∅
<b>Nutritional supplements vs placebo</b>											
Carnosine <sup>5</sup>	---	∅	∅	∅	---	---	---	---	---	∅	∅
CoQ10 <sup>6</sup>	∅	---	∅	---	---	---	---	---	---	---	∅
<b>Psychological, exercise, or multi-component interventions</b>											
CBT <sup>a7</sup>	★★	★★	★★	★★	★★	---	---	---	---	---	∅
Exercise <sup>a7</sup>	★★	★★	★★	★★	★★	---	---	---	---	---	∅
CBT + Exercise in combination <sup>a7</sup>	★★	★★	★★	★★	★★	---	---	---	---	---	∅
Detox regimen <sup>b8</sup>	∅	∅	---	∅	∅	---	∅	---	---	---	∅
Mindfulness-based stress reduction <sup>b9</sup>	---	★	★	★	---	★	---	★	---	---	---
Sleep focused mind-body bridging <sup>c10</sup>	∅	∅	∅	★	∅	★	∅	★	★	---	---
<b>Other interventions</b>											
Acupuncture <sup>a11</sup>	∅	∅	---	---	---	---	---	---	---	---	∅
CPAP <sup>d12</sup>	★	★	★	★	★	---	---	---	★	---	---

Shading represents the direction of effect: Pale yellow=Mixed Findings/Unclear, Green=Evidence of benefit, Gray=No association, Red=Favors usual care

Symbols represent the strength of the evidence: --- No evidence, Ø Insufficient, ★Low, ★★ Moderate, ★★★ High

<sup>a</sup> Versus usual care/TAU

<sup>b</sup> Versus waitlist

<sup>c</sup> Versus sleep education

<sup>d</sup> Versus sham CPAP

## CONCLUSION

We found a small but growing body of evidence examining a disparate array of treatments for Veterans with GWI. There is low- to moderate-strength evidence that suggests several treatments may hold promise for improving symptoms related to GWI: the evidence was moderate-strength for benefits of a combination of CBT and exercise and low-strength for 2 distinct mindfulness-based interventions and CPAP for Veterans with GWI who have sleep-disordered breathing. Doxycycline, on the other hand, is likely to be an ineffective treatment and is associated with harms (moderate-strength evidence). There are 33 ongoing, single-arm pilot, or unpublished studies examining a variety of interventions: some of these studies will help strengthen the evidence base for interventions that have already been examined on a small scale (eg, CBT and mindfulness-based stress reduction). However, many of these studies examine interventions that are both different from each other and different from interventions that have been studied before. While this approach may help identify potentially promising interventions, the variety of treatments examined will make it challenging to develop enough of an evidence base to guide clinicians about which treatments are most likely to be effective in clinical practice and which treatments should be avoided. Part of the challenge in studying treatment of GWI is the lack of an agreed-upon case definition, and the heterogeneity of symptoms and differing degrees of functional impairment experienced by those with GWI. Addressing these issues will help researchers to better target intervention-focused research.