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

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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.

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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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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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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.

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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_{10} (CoQ10), acupuncture, and detoxification, though the SOE for these findings was insufficient to draw

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

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
[a] Versus usual care/TAU
[b] Versus waitlist
[c] Versus sleep education
[d] 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.

ABBREVIATIONS TABLE

Abbreviation	Definition
A	Actual
AA	African American
AMED	Allied and Complementary Medicine Database
BAC-A	Brief Assessment Checklist for Adolescents
BDI	Beck Depression Inventory
BID	*bis in die*
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
BSI	Brief Symptom Inventory
BSS	Bowel Symptom Scale
BVMT-R	Brief Visuospatial Memory Test-Revised
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CBC	Complete Blood Count
CBT	Cognitive Behavioral Therapy
CBTi	Cognitive Behavioral Therapy for Insomnia
CCRCT	Cochrane Central Register of Controlled Trials
CDC	Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Programs
CDSMP	Chronic Disease Self-Management Program
CDSR	Cochrane Database of Systematic Reviews
CES-D	Center for Epidemiological Studies-Depression Scale
CFQ	Cognitive Failures Questionnaire
CFQ11	Chalder Fatigue Scale
CFS	Chronic Fatigue Syndrome
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMI	Chronic Multisymptom Illness
CoE	Center of Excellence for Research on Returning War Veterans
CoQ10	Coenzyme Q_{10}
COWAT	Controlled Oral Word Association Test
CPAP	Continuous Positive Airway Pressure
CPT	Connors Continuous Performance Test
CPT-3	Conner's Continuous Performance Test - 3rd Edition
CRS	Chronic Rhinosinusitis
CVLT-II	California Verbal Learning Test Second Edition
DB-RCT	Double-Blind Randomized Controlled Trial
DCS	D-cycloserine
D-KEF	Delis-Kaplan Executive Function System
DoD	Department of Defense
DTI	Diffusion Tensor Imaging

Abbreviation	Definition
DTS	Davidson Trauma Scale
E	Estimated
EBM	Evidence-based Medicine
EEG	Electroencephalogram
AE	Adverse event
EHR	Electronic health record
EMG	Electromyography
ERP	Event Related Potential
ESP	Evidence Synthesis Program
f	Cohen's f Value
FIQR	Revised Fibromyalgia Impact Questionnaire
FIT	Rey 15-Item Test
FODMAP	Fermentable Oligo-, Di-, Mono-saccharides And Polyols
FSS	Fatigue Severity Scale
GAD-7	Generalized Anxiety Disorder 7-item
GI	Gastrointestinal
GW	Gulf War
GWHE	Gulf War Health Education
GWI	Gulf War Illness
GWV	Gulf War Veteran
GWVI	Gulf War Veterans Illness
HA	Headache
HADS	Hospital Anxiety and Depression Scale
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HD-tDCS	High Definition transcranial Direct Current Stimulation
HIT-6	Headache Impact Test
HPG	Hypothalamic-Pituitary-Gonadal
HPT	Hypothalamic–Pituitary–Thyroid
HRQoL	Health-Related Quality of Life
HVLT-R	Hopkins Verbal Learning Test – Revised
IBS	Irritable Bowel Syndrome
IBS-QoL	Irritable Bowel Syndrome Quality of Life
ICTRP	International Clinical Trials Registry Platform
IQR	Interquartile Range
ISI	Insomnia Severity Index
LDLPFC	Left Dorsolateral Prefrontal Cortex
LED	Light Emitting Diode
LMC	Left Motor Cortex
MA	Meta-Analysis
MAP	Mean Arterial Pressure
MASQ	Mood and Anxiety Symptoms Questionnaire

Abbreviation	Definition
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MBB	Mind-Body Bridging
MBSR	Mindfulness-based Stress Reduction
MCS	Mental Component Summary
MFI-20	Multidimensional Fatigue Inventory-20
MFSI	Multidimensional Fatigue Symptom Inventory
MPI	Multidimensional Pain Inventory
MPQ	McGill Pain Questionnaire
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MSG	Monosodium glutamate
NI	Nasal Irrigation
NR	Not Reported
NRCT	non-Randomized Controlled Trial
NSI	Neurobehavioral Symptom Inventory
ORD	Office of Research and Development
P	P-Value
PCL	PTSD Checklist
PCS	Physical Component Summary
PDI	Pain Disability Index
PFS	Piper Fatigue Scale
PHQ	Patient Health Questionnaire
PICOTS	Population, interventions, comparators, outcomes, timing, and setting
preSMA	Presupplementary Motor Area
PRESS	Peer Review of Search Strategies
PROMIS	Patient Reported Outcomes Measurement Information System
PSQI	Pittsburgh Sleep Quality Index
PSS-I	PTSD Symptom Score interview
pts	Participants
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of Life
RCT	Randomized Controlled Trial
ROB	Risk of Bias
rTMS	Repetitive Transcranial Magnetic Stimulation
SAT	Symptoms Assessment Tool
SCL-90R	Symptom Checklist-90-Revised
SD	Standard Deviation
SE	Standard Error
SED	Sleep Education
SF-12V	Standard Form 12-Veteran version
SF-36	36-Item Short Form Health Survey
SF-MPQ	Short-Form McGill Pain Questionnaire

Abbreviation	Definition
SNOT-20	Sinonasal Outcome Test-20
SOE	Strength of Evidence
SORT	Semantic Object Retrieval Test
SR	Systematic Review
TAU	Treatment as Usual
tDCS	Transcranial Direct Current Stimulation
TEP	Technical Expert Panel
TMT	Trail Making Test
Tx	Treatment
USA	United States of America
VA	Veterans Affairs
VAMC	Veterans Affairs Medical Center
VAS	Visual Analog Scale
VHA	Veterans Health Administration
VNS	Vagus Nerve Stimulation
VSF-36	Veterans 36-Item Short Form
VSL	Very Safe Lactobacilli
WAIS-IV	Wechsler Adult Intelligence Scale-Fourth Edition
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule
WRIISC	War Related Illness and Injury Study Center

EVIDENCE REPORT

INTRODUCTION

After the 1990-1991 conflict in the Persian Gulf, many Gulf War Veterans began reporting numerous unexplained symptoms including, but not limited to, systemic pain, fatigue, flu-like symptoms and difficulty with memory/concentration. These symptom clusters were initially classified as Persian Gulf War Syndrome, then more generally under the broader umbrella of Chronic Multisymptom Illness (CMI), and most recently as Gulf War Illness (GWI).[13] The 2 most widely recognized case definitions of GWI —recommended for use by the Department of Defense (DoD) and Department of Veterans Affairs (VA)—are the Centers for Disease Control and Prevention (CDC)[14] and Kansas[15] definitions. The CDC definition defines a case as having at least 1 symptom from 2 of 3 categories (fatigue, mood and cognition, and musculoskeletal) for 6 months or longer.[14] The Kansas approach defines a case as having 1 moderately severe, or 2 or more chronic, symptoms in at least 3 of 6 domains (including fatigue or sleep, pain, neurologic or cognitive or mood, gastrointestinal, respiratory, and skin).[15] While both case definitions require the onset of symptoms to be within 6 months of deployment, this onset criteria is not consistently applied. In addition, a wide range of symptom severity and functional impairment is captured by the current case definitions. The proportion of Gulf War-deployed Veterans who meet case criteria for GWI is approximately 34% (based on the Kansas case definition) to as high as 60% (based on the less-restrictive CDC case definition).[16] While the etiology of GWI is still debated, as many as 250,000 former service members may suffer from GWI,[17] making the need for treatment urgent.

Identification and treatment of GWI is a top research priority for the VA Office of Research and Development (ORD). Although the VA and DoD developed an evidence-based clinical practice guideline for the management of CMI in 2014,[18] only 3 of the identified trials investigated treatment of GWI specifically (other CMI conditions reviewed included chronic fatigue syndrome, irritable bowel syndrome, and fibromyalgia, and included non-Veteran populations). The VA and other institutions have recently provided funding for numerous trials of treatments and management strategies for GWI, and the research in this area is rapidly expanding. An updated, systematic evidence review that focuses on the treatment of GWI in Gulf War Veterans is needed to understand this emerging body of evidence and assist Veterans Health Administration (VHA) leadership in developing and funding future clinical and research priorities.

This systematic review seeks to expand on recent work by identifying potentially promising interventions for the treatment of GWI and its related symptoms as well as identifying any areas that have been relatively well-studied and shown to be ineffective or harmful. Together, this will help target resources for further inquiry.

METHODS

TOPIC DEVELOPMENT

The key research questions for the review were as follows:

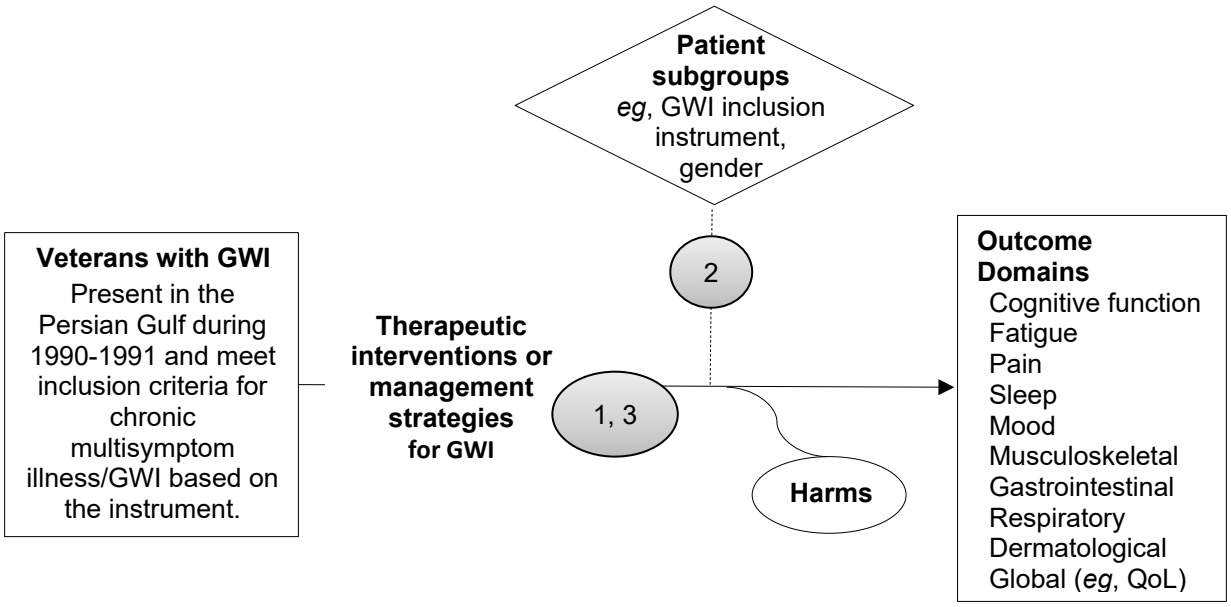
1. Evidence on effectiveness/harms: What are the benefits and harms of pharmacological and non-pharmacological interventions and management strategies for Veterans with GWI?

2. Evidence about subgroups: Do the effects of the interventions differ among subgroups Veterans with GWI in direct comparison with a larger sample of GWI patients?

3. Emerging research: What interventions for GWI have been examined in:
   a) noncomparative studies only?
   b) ongoing/unpublished trials or cohort studies?

Our approach was guided by the conceptual framework we developed in consultation with our operational partners (Figure 1).

Figure 1. Conceptual framework



Note. Numbers in grey bubbles refer to Key Questions
Abbreviations: GWI=Gulf War Illness; QoL=quality of life

SEARCH STRATEGY

We conducted a primary review of the literature by systematically searching, reviewing, and analyzing the scientific evidence as it pertains to the research questions. To identify relevant articles, we searched Ovid MEDLINE, Ovid PsycINFO, Ovid EBM Reviews (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), CINAHL, and Allied and Complementary Medicine Database (AMED) through September 17, 2019. Search strategies were developed in consultation with a research librarian, and peer reviewed by a second research librarian using the instrument for Peer Review of Search Strategies (PRESS).[19] The search strategy included terms to identify Veterans from the Gulf War era (*eg*, Desert Shield, Desert Storm, Kuwait War, Operation GRANBY) combined with past and present terms to identify Gulf War Illness (*eg*, chronic multisymptom illness, chronic fatigue, Gulf War Syndrome). We limited our search to English-language publications but did not limit by publication status or study design. To identify in-progress or unpublished studies, we searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; the full search strategies are in Appendix A). We reviewed the bibliographies of relevant articles and contacted experts to identify additional studies.

STUDY SELECTION

Criteria for population, interventions, comparators, outcomes, timing, and setting (PICOTS; Table 1) were developed in collaboration with our operational partners and Technical Expert Panel. Two ESP-reviewers independently assessed studies for inclusion based on pre-specified criteria. All discordant results were resolved through consensus or consultation with a third ESP-reviewer. Articles meeting eligibility criteria were included for data abstraction.

For evidence on effectiveness, harms, and subgroups, eligible study designs included RCTs, nRCTs, and cohort studies in Veterans with GWI that directly compared interventions against each other, placebo, or usual care. To be included, both the intervention and comparator groups had to consist of a population of Veterans with GWI. If there was a mix of participants with and without GWI, we only included the study if the GWI population was analyzed separately. For Key Question (KQ) 3 on emerging research, we also included noncomparative intervention studies such as pilot/feasibility studies or case series.

Table 1. PICOTS by Key Question

Key Question:	KQ1. evidence on effectiveness and harms: What are the (a) benefits and (b) harms of interventions and management strategies for Veterans with GWI?	KQ2. evidence about subgroups: Do the effects of the interventions differ among subgroups in direct comparison with a larger sample of GWI patients?	KQ3. emerging research: What interventions for GWI have been examined in: a) noncomparative studies only? b) ongoing/unpublished trials or cohort studies?
Population	Veterans with GWI who were deployed to the Persian Gulf region between Aug 2, 1990 - Nov 1991. Include international Veteran populations (countries that deployed troops there*; but limit to English-language publications). Include studies of civilian contractors present during the conflict, if available. Include studies where deployment status is unclear because diagnosis was made according to CDC/Fukuda 1998 criteria.[14]	Subpopulations may include but are not limited to the following: - Gender - Case definition - Severity of symptoms - Branch of military Studies that include only members of a specific subgroup and do not compare findings to Veterans with GWI overall would address KQ1 only.	Veterans with GWI who were deployed to the Persian Gulf region between Aug 2, 1990 - Nov 1991. Include international veteran populations (countries that deployed troops there*; but limit to English-language publications). Include studies of civilian contractors present during the conflict, if available. Include studies where deployment status is unclear because diagnosis was made according to CDC/Fukuda 1998 criteria.[14]
Intervention	Pharmacological and nonpharmacological interventions or management strategies for Gulf War Illness		
Comparators	Another active intervention, placebo, or usual care.		Another active intervention, placebo, usual care, or no comparator (*eg*, single-arm pilot study).
Outcomes	Outcomes of interest are the 3 symptom domains that occur in both the CDC and Kansas case definitions: cognitive function, fatigue, and pain. Other outcomes of interest: • Additional symptom domains used in the Kansas case definition (sleep, mood, musculoskeletal, gastrointestinal, respiratory, dermatological) • Global outcomes (*eg*, QoL and measures of function) • PTSD • Adverse effects of treatment		
Timing	No limits		
Settings	No limits		
Study Design	RCT, nRCT, cohort, SRs/MAs		Unpublished or in-progress comparative studies (RCT, nRCT, cohort, SRs/MAs) and case series/single-arm pilot studies of interventions not examined in comparative studies. Exclude case reports.

*We recognize other countries may use different case definitions

Abbreviations: CDC=Centers for Disease Control and Prevention; GWI=Gulf War Illness; KQ=Key Question; MA=Meta-Analysis; nRCT=non-Randomized Controlled Trial; PTSD=Posttraumatic Stress Disorder; QoL=Quality of Life; RCT=Randomized Controlled Trial; SR=Systematic Review

DATA ABSTRACTION

Data from studies meeting inclusion criteria were abstracted by 1 ESP reviewer and confirmed by at least 1 additional ESP reviewer. From each study, we abstracted the following where available: study design, sample size, setting, population characteristics, participant inclusion and exclusion criteria, the study and comparator interventions including dosage, timing, and duration of treatment, duration of follow-up, adjunctive interventions, adverse effects, and findings according to GWI outcome domains (cognitive function, fatigue, pain, sleep, mood, QoL, musculoskeletal, gastrointestinal, respiratory, and dermatological).

QUALITY ASSESSMENT

Two ESP-reviewers independently assessed the risk of bias (ROB) of each study. To assess the ROB of RCTs we used the Revised Cochrane Risk-of-Bias criteria, RoB 2.0.[20] Disagreements were resolved by consensus or a third ESP-reviewer. The ROB assessment criteria and our ratings for each study are shown in Appendix C.

DATA SYNTHESIS

We qualitatively synthesized the evidence and compiled evidence tables of study characteristics and findings for each key question, grouping outcomes and interventions across studies when indicated. We were not able to conduct meta-analyses of interventions because there were not enough studies with similar characteristics of similar interventions to allow meaningful quantitative analysis.

RATING THE BODY OF EVIDENCE

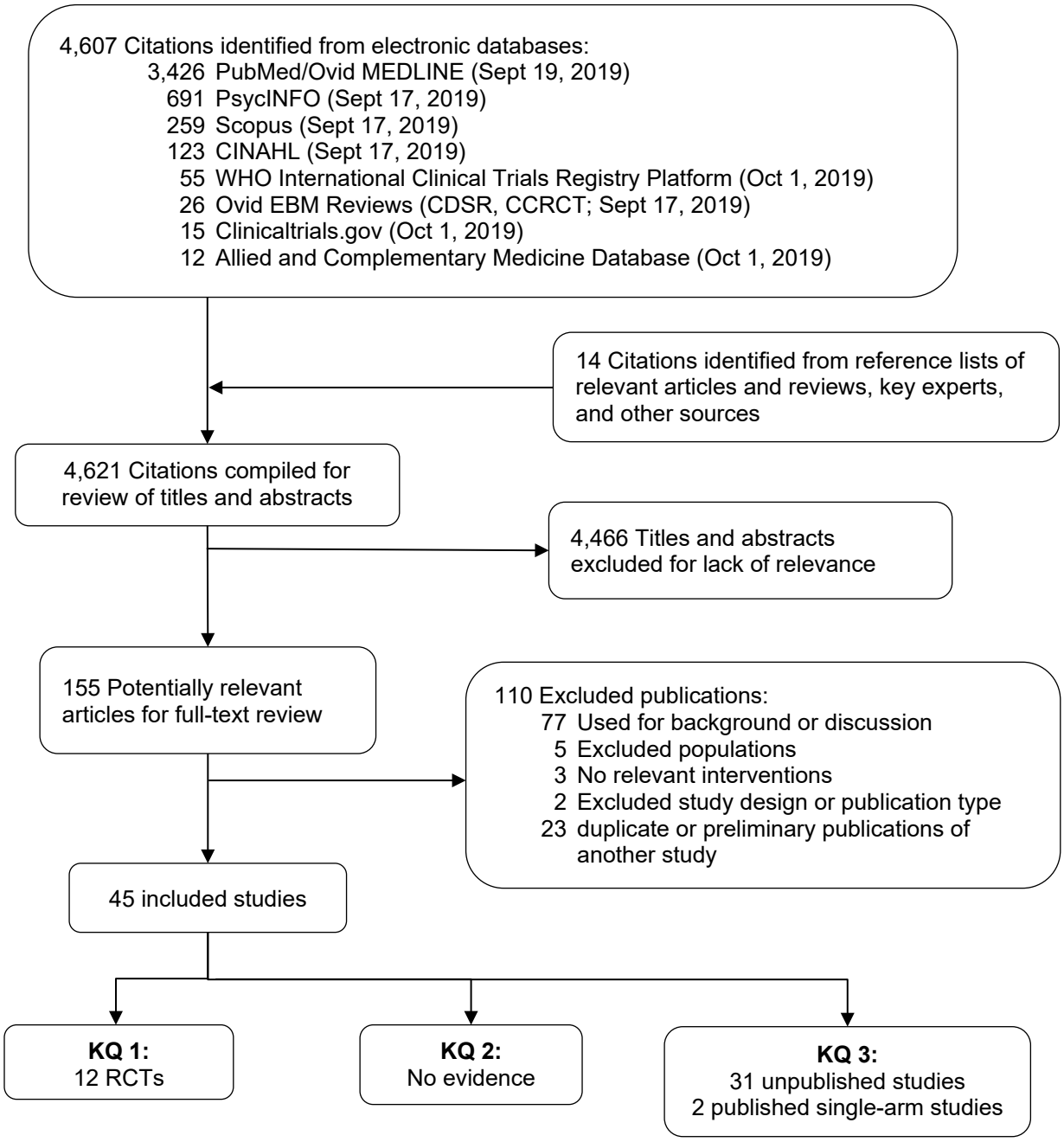
We assessed the overall strength of evidence (SOE) for each outcome using a method developed for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPCs).[21] The AHRQ EPC method considers study limitations, directness, consistency, precision, and reporting bias to classify the SOE for individual outcomes independently for RCTs and observational studies, with supplemental domains of dose-response association, plausible confounding that would decrease the observed effect, and strength of association, as well as separate guidance for applicability.[22] Ratings were categorized as follows:

- High=Very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies, the findings are stable, and another study would not change the conclusions.
- Moderate=Moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies and the findings are likely to be stable, but some doubt remains.
- Low=Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient=Unable to estimate an effect, typically because there were too few studies, with very small sample sizes, and often with methodologic flaws.
- No evidence=No studies.

RESULTS

We reviewed a total of 4,621 citations. After title and abstract review, 155 met inclusion criteria. After we reviewed the full text of these studies, we included a total of 45 studies. A diagram of the literature yield is shown in Figure 2.

Figure 2. Literature Flow Chart



Abbreviations: CCRCT=Cochrane Central Register of Controlled Trials; CDSR=Cochrane Database of Systematic Reviews; CINAHL=Cumulative Index to Nursing and Allied Health Literature; EBM=Evidence-based Medicine; KQ= Key Question; RCT=Randomized Controlled Trial; WHO=World Health Organization

Twelve RCTs addressed KQ1. The interventions included 4 medications (doxycycline,[1] mifepristone,[2] naltrexone,[3] and rifaximin[4]); 2 nutritional supplements (carnosine[5] and CoQ10[6]); 4 studies with a behavioral or psychological treatment component (cognitive behavioral therapy [CBT] with and without exercise,[7] a detox regimen,[8] and 2 mindfulness-based interventions[9,10]); acupuncture[11]; and continuous positive airway pressure therapy (CPAP).[12]

Four interventions were examined in specific subpopulations of GWI patients: doxycycline in patients positive for mycoplasma DNA,[1] rifaximin in patients with irritable bowel syndrome (IBS),[4] mind-body bridging (MBB) in patients with sleep disturbance,[10] and CPAP in patients with sleep-disordered breathing.[12] In a study of mindfulness-based stress reduction (MBSR), patients diagnosed with posttraumatic stress disorder (PTSD) made up a large proportion (81.8%) of the sample, and the effect of the intervention on PTSD symptoms was evaluated specifically in this subgroup.[9]

Although the findings of these studies may be most applicable to the targeted subpopulations, none of the studies identified in our search addressed KQ2 by comparing the effects of an intervention in the subpopulation with a broader sample of GWI patients. Additionally, although considered eligible in our selection criteria, our search did not yield any cohort studies that addressed the key questions.

For KQ3, we compiled information from 31 intervention studies that are ongoing or unpublished, as well as 2 published single-arm intervention studies. In describing the current research on interventions, we also included 2 studies that were terminated before completion[23,24] due to low enrollment or for unspecified reasons.

The findings for each KQ are presented in the sections that follow.

KEY QUESTION 1: What are the benefits and harms of pharmacological and non-pharmacological interventions and management strategies for Veterans with GWI?

Table 2 provides descriptive characteristics about each of the 12 trials that addressed KQ1, including the interventions and comparators used, the duration of treatment, the duration of observation (which includes the treatment period), the populations studied, and the outcomes reported.

The outcomes measured varied among the studies (Table 2). Measures of physical health, pain, and cognitive function were reported most frequently. None of the included studies reported outcomes specifically for respiratory, dermatological, or musculoskeletal symptoms measured separately from overall pain.

Most of the studies used the CDC or Kansas criteria for defining GWI. Some studies used equivalent criteria or modified the CDC or Kansas criteria. One study of rifaximin[4] included Gulf War Veterans with IBS.

Following Table 2, we provide a summary of the findings for each intervention, organized into 4 categories: medications, nutritional supplements, behavioral/exercise/multicomponent, and other interventions. Detailed findings on effectiveness and adverse events are provided in Appendix D, Tables 9-12.

Table 2. Characteristics of randomized controlled trials of interventions for Gulf War Illness

Study *Design* *Setting* *Years of enrollment* *N=total participants* *Overall ROB*	**Intervention vs comparator** *Dose* *N randomized Tx vs C* *Duration of treatment and observation (includes treatment period)*	**Population** *GWI case definition* *Subpopulation, if applicable* *Age: Mean (SD)* *Female: %* *Race: % White/Afr Am/Other* *Hispanic: %* *Employed full-time: %* *Clinical characteristics*	**Outcomes reported[a]**										
			Physical health overall	***Pain***	***Cognitive***	***Fatigue***	***Mental health overall***	***Depression***	***Global outcomes[b]***	***PTSD symptoms***	***Sleep***	***GI symptoms***	***Adverse events***
Medications													
Doxycycline[1] DB-RCT Multisite: 26 VA and 2 DoD medical centers Years: April 1999-Nov 2001 N=491 ROB: Low	Doxycycline 200 mg/day vs placebo N=245 vs 246 Tx duration: 12 months Observation: 18 months	CDC criteria Subpop: mycoplasma DNA positive Tx group only: Age: 41.1 (9.2) Female: 15.5 Race: 61.6 / 26.5 / 7.8 Hispanic: NR Employed: 73.5	X	X	X	X	X	---	---	---	---	---	X
Mifepristone[2] DB-RCT, crossover Single site, VA hospital 2008-2011 N=36 ROB: Some concerns	Mifepristone 200 mg/day vs placebo Two, 3-week crossover Tx phases with 1-month washout N=18 vs 18 in phase 1 18 vs 15 in phase 2 Tx duration: 6 weeks Observation: 4 months	Kansas criteria Age: 49.1 (7.2) Female: 0.0 Race: 40.6 / 50.0 / 9.4 Hispanic: 50.0 Employed: 56.3	X	---	X	X	X	X	---	X	---	---	X
Naltrexone[3] RCT, Pts blinded Setting: NR Years: NR N=40 ROB: High	Naltrexone 4.5 mg/day vs placebo 3-month crossover Tx phases separated by 1-month washout. N=37 (completed both phases) Tx duration: 3 months Observation: 7 months	Kansas, modified Age: 54 (SD NR) Female: 2.7 (completed study) Race: NR Employed: NR	X	---	X	---	---	---	---	---	---	---	X
Rifaximin[4] DB-RCT Setting: NR Years: NR N=50 ROB: Some concerns	Rifaximin (550 mg 2x/d) vs placebo N=27 vs 23 Tx duration: 2 weeks Observation: 2 weeks	GWI criteria: NR Subpopulation: IBS (Rome III) Tx group only: Age, median: 53 Female: 13.6 Race: NR Employed: NR	---	---	---	---	---	---	X	---	---	X	X

Study *Design* *Setting* *Years of enrollment* *N=total participants* *Overall ROB*	**Intervention vs comparator** *Dose* *N randomized Tx vs C* *Duration of treatment and observation (includes treatment period)*	**Population** *GWI case definition* *Subpopulation, if applicable* *Age: Mean (SD)* *Female: %* *Race: % White/Afr Am/Other* *Hispanic: %* *Employed full-time: %* *Clinical characteristics*	**Outcomes reported[a]**										
			Physical health overall	***Pain***	***Cognitive***	***Fatigue***	***Mental health overall***	***Depression***	***Global outcomes[b]***	***PTSD symptoms***	***Sleep***	***GI symptoms***	***Adverse events***
Nutritional supplements													
Carnosine[5] DB-RCT Single site: Georgetown Univ Hospital 2008-2011 N=34 ROB: High	L-carnosine (dose of 500, 1,000, 1,500 mg/d increasing at 4-week intervals) vs placebo N=34 (only 12 vs 13 finished study) Tx duration: 12 weeks Observation: 14 weeks	CDC criteria, or GW Vet diagnosed with post-GW CFS Of 25 study completers: Age: 49.4 Female: 32 Race: NR Employed: NR	---	X	X	X	---	---	---	---	---	X	X
CoQ10[6] DB-RCT Setting: Southern California Hospital Years: NR N=46 ROB: High	CoQ10 (2 dosage arms, 100 mg/day vs 300 mg/day) vs placebo N=11 vs 12 vs 23 Tx duration: 3.5 +/- 0.5 months Observation: 3.5 +/- 0.5 months	Required both CDC & Kansas criteria Placebo vs Q100 vs Q300: Age: 48 vs 50 vs 44 Female: 9 vs 27 vs 17 White: 55 vs 73 vs 58 Latino: 18 vs 0 vs 17 Afr Am: 9.1 vs 9.1 vs 25 Employed: NR	X	---	X	---	---	---	---	---	---	---	X
Psychological, exercise, or multi-component interventions													
CBT + Exercise[7] 2x2 factorial RCT, Pts not blinded Multi-site: 18 VAs and 2 DoD medical centers April 1999-September 2001 N=1092 ROB: Some concerns	4 arms: CBT+Exercise (n=266) CBT only (n=286) Exercise only (n=265) TAU (n=270) Exercise sessions were 60 minutes and CBT sessions were 60 to 90 minutes; Each type of session held 1x/week. Tx duration: 12 weeks Observation: 12 months	CDC equivalent Age: 40.67 Female: 14.8 Race: 52.5 / 24.4 / 3.4 Hispanic: 19.6 Employed: NR	X	X	X	X	X	---	---	---	---	---	X
Detox regimen[8] RCT, Pts not blinded Commercial rehab center	Detox regimen: niacin immediate release (dose NR); then 20-30 min moderate aerobic exercise; then low temperature sauna (60-80 Celsius) 2-4 hours; other	Kansas criteria Sex: 66% Male, 34% Female Age: 51 (6.5) Race: 81 / 19 / 3	X	X	---	X	X	---	X	---	---	---	X

Study *Design* *Setting* *Years of enrollment* *N=total participants* *Overall ROB*	**Intervention vs comparator** *Dose* *N randomized Tx vs C* *Duration of treatment and observation (includes treatment period)*	**Population** *GWI case definition* *Subpopulation, if applicable* *Age: Mean (SD)* *Female: %* *Race: % White/Afr Am/Other* *Hispanic: %* *Employed full-time: %* *Clinical characteristics*	**Outcomes reported[a]**										
			Physical health overall	***Pain***	***Cognitive***	***Fatigue***	***Mental health overall***	***Depression***	***Global outcomes[b]***	***PTSD symptoms***	***Sleep***	***GI symptoms***	***Adverse events***
2013-2015 N=32 ROB: Some concerns	vitamin/mineral supplements in calcium-magnesium drink throughout; vs waitlist N=22 vs 10 Tx duration: 4-6 weeks Observation: 3 months	Hispanic: NR Employed: 59											
Mindfulness-based stress reduction[9] RCT, Pts not blinded Setting: VA Hospital Years: NR N=55 ROB: Some concerns	MBSR: 2.5 sessions 1x/week for 8 weeks + single 7-hour weekend session vs TAU N=26 vs 29 Tx duration: 8 weeks Observation: 6 months	CDC criteria Subpopulation: PTSD 81.8%; ≥50% service-connected disability 79.6% Age: 49.9 Female: 14.5 Race: 61.8 / 18.2 / 14.5 Hispanic: NR Employed: NR	---	X	X	X	---	X	---	X	---	---	---
Sleep-focused Mind-Body Bridging[10] Study design: Prospective RCT Single site: VA Salt Lake City 2012-2015 N=60 ROB: Some concerns	Sleep-focused MBB vs sleep education (SED; lectures, group discussions) N=33 vs 27 Tx duration: 3 sessions over 3 weeks Observation: 3 months Pts could remain on previously prescribed sleep medications.	CDC equivalent Subpopulation: sleep disturbance Age: 50.7 Female: 10.0 Race: 88.0 / 7.0 / 8.6 Hispanic: 8.3 Employed: NR	X	X	X	X	X	X	X	X	X	---	---
Other interventions													
Acupuncture[11] RCT, Pts not blinded 30 treatment sites Enrolled 2010-2013 N=104 ROB: Some concerns	Acupuncture 2x/week for 6 months vs waitlist 2 months, then acupuncture 1x/week for 4 months N=52 vs 52 Tx duration: 6 months Observation: 6 months	CDC criteria Age: 48.2 Female: 13.0 Race: 80.7 / 9.6 / 9.6 Hispanic: 5.8 Employed: NR	X	X	---	---	---	---	---	---	---	---	X
CPAP[12] RCT, Pts blinded	Active nasal CPAP (using individualized pressure level that eliminated inspiratory	Kansas equivalent Subpopulation: sleep-disordered	X	X	X	X	X	---	---	---	X	---	---

Study *Design* *Setting* *Years of enrollment* *N=total participants* *Overall ROB*	**Intervention vs comparator** *Dose* *N randomized Tx vs C* *Duration of treatment and observation (includes treatment period)*	**Population** *GWI case definition* *Subpopulation, if applicable* *Age: Mean (SD)* *Female: %* *Race: % White/Afr Am/Other* *Hispanic: %* *Employed full-time: %* *Clinical characteristics*	**Outcomes reported[a]**										
			Physical health overall	***Pain***	***Cognitive***	***Fatigue***	***Mental health overall***	***Depression***	***Global outcomes[b]***	***PTSD symptoms***	***Sleep***	***GI symptoms***	***Adverse events***
Single site, VA hospital. January 2006-July 2008 N=18 ROB: Low	airflow limitation) vs sham CPAP (pressure below 1 cm H_20) N=9 vs 9 Tx duration: 5+ hours/ night for 3 weeks Observation: 3 weeks	breathing Age: 42 (4) Female/Race/Employed: NR Apnea Hypopnea Index: 19 (25) Respiratory event-related arousal: 15 (10) Ptherapeutic (parallel level of nasal CPAP that eliminates inspiratory airflow limitation): 9 (2) cmH_2O											
		Total studies reporting outcome	**9**	**9**	**9**	**8**	**7**	**4**	**4**	**3**	**2**	**2**	**9**

[a] No outcomes were reported for musculoskeletal, respiratory, or dermatological symptoms.

[b] Include measures of functional status and quality of life.

Abbreviations: CBT=Cognitive Behavioral Therapy; CDC=Centers for Disease Control and Prevention; CFS=Chronic Fatigue Syndrome; CoQ10=Coenzyme Q10; CPAP=Continuous Positive Airway Pressure; DB-RCT=Double Blind Randomized Controlled Trial; DoD=Department of Defense; GI=Gastrointestinal; GW=Gulf War; GWI=Gulf War Illness; IBS=Irritable Bowel Syndrome; MBB=Mind-Body Bridging; MBSR=Mindfulness-based Stress Reduction; NR=Not Reported; Pts=Participants; PTSD=Posttraumatic Stress Disorder; QoL=Quality of Life; ROB=Risk of Bias; SD=Standard Deviation; SED=Sleep Education; TAU=Treatment as Usual; Tx=Treatment; VA=Veterans Affairs

Medications

We found 4 trials of medications (doxycycline,[1] mifepristone,[2] naltrexone,[3] and rifaximin[4]; Table 3; Study characteristics in Table 2; Detailed results in Appendix D, Tables 9-11). A large (N=491), adequately-powered, 12-month study of doxycycline (200 mg/day) provided moderate-strength evidence of no benefit and greater risk of adverse effects, such as nausea and photosensitivity, with treatment compared with placebo.[1] Study retention in the doxycycline group was similar to that of the placebo group (80% versus 82.5%), and adherence was rated "good or excellent" in 77.5% versus 74.5% of participants at 6 months, and 65.6% versus 66.6% at 12 months.[1] A 2-week study of rifaximin[4] (550 mg twice per day) in patients with IBS found no effect on IBS symptoms or quality of life; we rated the evidence insufficient because there was only 1 small study that analyzed only the participants who completed treatment (92.6% in rifaximin vs 82.6% placebo). Studies of mifepristone[2] (200 mg/day for 3 weeks) and naltrexone[3] (4.5 mg/day for 3 months) were rated as insufficient due to methodologic limitations such as small sample size[2] and concerns with allocation concealment[3] (more details on quality are presented in Appendix C, Table 8; Information on harms is in Table 12). Attrition was low in both studies, with 97% of randomized participants completing treatment in the mifepristone study[2] and 92.5% completion in the naltrexone study.[3]

Table 3. Summary of the effectiveness and strength of evidence from placebo-controlled trials of medications for treating symptoms of Gulf War Illness

	Doxycycline[1]	Mifepristone[2]	Naltrexone[3]	Rifaximin[4]
Study characteristics				
Sample size	N=491	N=36	N=40	N=50
ROB	Low	Some concerns	High	Some concerns
Summary of effectiveness (strength of evidence) of treatment vs placebo, by symptom domain				
Physical health overall	No difference (Moderate)	No difference (Insufficient)	No difference (Insufficient)	---
Pain	No difference (Moderate)	---	---	---
Cognitive	No difference (Moderate)	Mixed findings (Insufficient)	No difference (Insufficient)	---
Fatigue	No difference (Moderate)	No difference (Insufficient)	---	---
Mental health overall	No difference (Moderate)	No difference (Insufficient)	---	---
Depression	---	No difference (Insufficient)	---	---
Global outcomes function, QoL	---	---	---	No difference (Insufficient)
PTSD symptoms	---	No difference (Insufficient)	---	---

	Doxycycline[1]	Mifepristone[2]	Naltrexone[3]	Rifaximin[4]
Sleep	---	---	---	---
GI symptoms	---	---	---	No difference (Insufficient)
Adverse events	Favors placebo (Moderate)	Unclear (Insufficient)	Unclear (Insufficient)	No difference (Insufficient)

Abbreviations: GI=Gastrointestinal; N=Number of participants; PTSD=Posttraumatic Stress Disorder; QoL=Quality of Life; ROB=Risk of bias; SOE=Strength of Evidence

Nutritional supplements

Two high-ROB trials of nutritional supplements (carnosine[5] and CoQ10[6]) found some evidence of benefit on various GWI symptoms (Table 4; Study characteristics in Table 2; Detailed results in Appendix D). The SOE for these findings is insufficient due to methodologic limitations including selective outcome reporting in the CoQ10 trial[6] and potential deviation from the intended interventions in the carnosine trial.[5]

The trial of carnosine (500 mg/day increasing to 1500 mg/day over 12 weeks) in 34 patients with IBS found positive effects on cognitive function and gastrointestinal (GI) symptoms, but no difference on pain and fatigue (see Appendix D).[5] At 12 weeks, the proportion of participants with no IBS symptoms increased from 30% to 43% compared with baseline in the carnosine group, but remained 33% in the placebo group (P = 0.019). Symptoms of stool frequency and watery consistency reduced with carnosine but did not change with placebo. The carnosine group had significantly lower WAIS-R scores at week 12 compared with placebo (P = 0.013). Because the WAIS-R scores were lower in the carnosine group at baseline, the effect of carnosine on cognitive symptoms is inconclusive. The authors report that study compliance was excellent based on diaries and pill counts, though this was not biologically verified. With regard to attrition, 9 of the 34 participants dropped out prior to the study ending (5 from the carnosine group and 4 from placebo). Two were terminated due to health issues determined to be unrelated to treatment, 4 were lost to follow-up, and 3 dropped out after 6 weeks due to "frustration about lack of improvement".[5]

A 4-month trial of CoQ10 (N = 46; n = 11 on 100 mg/day, n = 12 on 300 mg/day for 4 months) found improvement on overall physical health (differences in Summary Performance Score of 42% for 100 mg/day versus placebo [P = 0.025] and 15% for 300 mg/day versus placebo [P = 0.44]) but the threshold for improved versus not improved was not clearly defined.[6] No difference in cognitive symptoms was observed. Adherence was not reported for this trial. Attrition was minimal; 1 dropout in the treatment arm due to a stroke, and 3 in the placebo arm due to logistical reasons (2) and lost to follow-up (1).

Table 4. Summary of the effectiveness and strength of evidence from placebo-controlled trials of nutritional supplements for treating Gulf War Illness, by symptom domain

	Carnosine[5]	CoQ10[6]
Study characteristics		
Sample size	N=34	N=46
ROB	High ROB	High ROB
Summary of effectiveness (strength of evidence) of treatment vs placebo		
Physical health overall	---	Favors CoQ10 (Insufficient)
Pain	No difference (Insufficient)	---
Cognitive	Favors carnosine (Insufficient)	No difference (Insufficient)
Fatigue	No difference (Insufficient)	---
Mental health overall	---	---
Depression	---	---
Global outcomes (function, QoL)	---	---
PTSD symptoms	---	---
Sleep	---	---
GI symptoms	Favors carnosine (Insufficient)	---
Adverse events	No difference (Insufficient)	No difference (Insufficient)

Abbreviations: GI=Gastrointestinal; N=Number of Participants; PTSD=Posttraumatic Stress Disorder; QoL=Quality of Life; ROB=Risk of Bias; SOE=Strength of Evidence

Psychological, exercise, and multi-component interventions

This category of treatments for GWI includes 2 mindfulness-based interventions,[9,10] a detox regimen,[8] and a multi-arm trial of CBT with and without exercise[7] (see Table 2 for study characteristics; Table 5 for a summary of the evidence; and Appendix D, Tables 9-11 for detailed results). The 2 mindfulness approaches had somewhat inconsistent results. The first was a trial of MBSR (N = 55) – a program focused on increasing present moment awareness and acceptance of thoughts, emotions and sensations – which was delivered in 8 weekly, 2.5-hour sessions, plus 1 7-hour session.[9] It found that MBSR improves pain, cognitive functioning, fatigue, depression and PTSD symptoms among those with GWI compared to treatment as usual (TAU; low SOE). Improvements on all outcomes were retained at the 6-month follow up, with the exception of PTSD symptoms (detailed study information located in Table 2 and Appendix D).[9] Seventy-three percent of the intervention arm were classified as completers, defined as having attended 4 out of 8 classes. Attrition for TAU was not reported. Intention-to-treat (ITT) and completer analyses were performed and had similar results. With regard to follow-up data, 22 (85%) of those in the MBSR arm contributed 6-month follow-up data compared to 23 (79%) of those in the TAU arm.[9]

Another trial of a mindfulness-based approach, MBB (N = 60) taught participants to stay in the present moment when trying to fall asleep, as well as skills to manage stress and emotional reactivity to stressful thoughts over 3 sessions.[10] The comparator group received 3 Sleep Hygiene Educational (SED) sessions focused on improving routine and habits around sleep. MBB was found to improve fatigue, depression, PTSD and sleep, but did not improve overall physical or mental health, pain or cognitive functioning compared to SED. Of the initial 60 participants who were randomized to MBB (33) versus SED (27), 57 participants completed the intervention, indicated by their attending at least 2 sessions (31 [93.9%] versus 26 [96.3%]). A total of 55

completed the post assessment (29 [87.9%] versus 26 [93.9%]), and 49 completed the follow-up assessment (24 [72.7%] versus 25 [92.6%]). Reasons for attrition were not reported.[10]

In the trial of CBT and exercise,[7] 1,092 Veterans were randomly assigned to 1 of 4 groups: (1) TAU (n=271), which consisted of any and all care received from inside and outside the VA; (2) CBT and TAU (n=286) which added 12 weekly, 60-90 minute CBT group sessions that taught behavioral and cognitive skills to enhance coping and problem-solving; (3) TAU and exercise (n= 269) which added 12 weekly, 60-minute low-intensity aerobic exercise sessions; and (4) TAU with CBT and exercise (n= 266). Global physical health improvement was defined as a 7-point or greater increase on the Physical Component Scale (PCS) of the Veteran Short Form 36-Item Health Survey (VF-36). Among those who received CBT, exercise, or a combination of the 2, there was evidence of modest benefit (marginal effect) for up to 1 year after the intervention completion on several GWI symptom domains, including measures of physical health fatigue, cognitive functioning, distress, and mental health functioning (moderate SOE). The intervention adherence rates, defined as attending two-thirds of sessions, ranged from a low of 36% among those in the CBT only arm to a high of 47% for exercise only. Table 2 contains detailed study information, and results are in Appendix D.

Finally, the detox regimen study used a pragmatic, parallel design, to randomize 32 participants to either a daily regimen of exercise, sauna-induced sweating, crystalline nicotinic acid, and other supplements for 4-6 weeks (n=22) or waitlist control (n=10; Detailed study information located in Table 2, and results in Appendix D).[8] The intervention was found to improve pain, fatigue, and overall mental health, yet there was no difference on global QoL compared to placebo; methodological limitations such as limited sample size and selective outcome reporting inhibited our ability to have confidence in the conclusions. As such, outcomes from this detox regimen were all rated insufficient SOE. All 32 participants completed the intervention and 21 completed the 3-month follow up.[8]

The ROB for all psychosocial intervention studies was classified as “some concerns” primarily because of utilizing self-reported outcomes without blinding of participants as to which intervention group they were in. There are methodical ways to do this including using sham treatment as a control in some cases. We outline the pros and cons of such blinding procedures in the discussion. Another limitation of this body of literature is that the potential harms of these interventions were not well characterized – as was the case in the MBSR trial – or it was unclear whether the AEs were related to the intervention or not – as was the case in the CBT/Exercise trial. The detox intervention may place individuals at a higher risk of AEs; yet there may be promising effects of the mindfulness-based approaches and the combination of CBT and exercise (See Appendix C, Table 8 for ROB ratings, and Appendix D, Table 12 for AE details).

Table 5. Summary of the effectiveness and strength of evidence from trials of psychological, exercise, or multi-component interventions for treating GWI, by symptom domain

	CBT/Exercise/ combined CBT + Exercise[7]	Detox regimen[8]	Mindfulness-based stress reduction[9]	Sleep focused mind-body bridging[10]
Study characteristics				
Comparator	TAU	Waitlist	TAU	Sleep education
Sample size	N=1092	N=32	N=55	N=60
ROB	Some concerns	Some concerns	Some concerns	Some concerns
Summary of effectiveness (strength of evidence) of treatment vs comparator				
Physical health overall	Favors CBT (Moderate)	Mixed findings (Insufficient)	---	No difference (Insufficient)
Pain	Favors CBT; Favors combined CBT + exercise (Moderate)	Favors detox (Insufficient)	Favors MBSR (Low)	No difference (Insufficient)
Cognitive	Favors CBT; Favors exercise; Favors combined CBT + exercise (Moderate)	---	Favors MBSR (Low)	No difference (Insufficient)
Fatigue	Favors combined CBT + exercise (Moderate)	Favors detox (Insufficient)	Favors MBSR (Low)	Favors MBB (Low)
Mental health overall	Favors exercise; Favors combined CBT + exercise; Mixed findings CBT (Moderate)	Favors detox (Insufficient)	---	No difference (Insufficient)
Depression	---	---	Favors MBSR (Low)	Favors MBB (Low)
Global outcomes (function, QoL)	---	No difference (Insufficient)	---	No difference (Insufficient)
PTSD symptoms	---	---	Favors MBSR (Low)	Favors MBB (Low)
Sleep	---	---	---	Favors MBB (Low)
GI symptoms	---	---	---	---
Adverse events	Unclear (Insufficient)	Favors usual care (Insufficient)	---	---

Abbreviations: CBT=Cognitive Behavioral Therapy; GI=Gastrointestinal; MBB=Mind-body Bridging; MBSR=Mindfulness-based Stress Reduction; N=Number of Participants; PTSD=Posttraumatic Stress Disorder; QoL=Quality of Life; ROB=Risk of Bias; SOE=Strength of Evidence; TAU=Treatment as Usual

Other interventions (acupuncture, CPAP)

Two other interventions were identified (Table 6; Detailed study information in Table 2; and results in Appendix D). A trial of acupuncture[11] (N = 104) with some concerns for ROB found that overall physical health (P = 0.03; SE 3.76 [95% CI: 1.03 to 15.76]) and pain (P = 0.04; SE 1.71 [95% CI: -6.95 to -0.2]) significantly improved in the treatment arm versus wait list. Treatment consisted of individualized acupuncture protocols twice a week for 6 months compared to 2 months on a waitlist followed by once-weekly individualized acupuncture protocols. After 2 months, 90% of participants randomized to 2 sessions per week remained in the study, and 84.6% of those randomized to waitlist were available to receive treatment. Eighty-two percent (85 out of 104 randomized) completed the 6-month follow up assessment. Pain on needling was reported as an AE, but despite that, 96% of participants reported that they would recommend acupuncture.[11] The SOE was insufficient owing to lack of blinding with self-reported outcomes.

A low-ROB trial of CPAP among Veterans with GWI and sleep disordered breathing reported favorable results on multiple outcomes (low SOE).[12] The trial compared the use of CPAP at individualized pressure levels with sham CPAP (pressure below 1 cmH_2O) for 5 hours per night over 3 weeks. Although CPAP is an evidence-based treatment for sleep apnea, CPAP was also associated with improvement among a broader range of GWI symptoms in this study than just sleep outcomes. Specifically, significant improvements were found for pain (effect size: 2.14; P = 0.0008), fatigue (effect size: 2.55; P = 0.0002), cognitive function (effect size: 1.67; P = 0.004), sleep quality (effect size: 2.67; P = 0.0003), physical health (effect size: 2.79; P = 0.0003), and mental health (effect size: 1.29; P = 0.03). Compliance with assigned treatment was comparable between the active and sham groups (265.1 ± 90.2 minutes/night versus 266.6 ± 100.8 minutes/night, respectively; P = 0.98). Participants were 100% compliant with mailing back their questionnaires. One participant assigned to active treatment was enrolled in a PTSD treatment program and excluded. While methodologically the CPAP trial had low ROB, because the trial was small (N=18) more trials are needed to characterize the benefits with confidence.

Table 6. Summary of the effectiveness and strength of evidence from trials of acupuncture and CPAP in Veterans with Gulf War Illness

	Acupuncture[11]	CPAP[12]
Study characteristics		
Comparator	Waitlist	Sham CPAP
Sample size	N=104	N=18
ROB	Some concerns	Low ROB
Summary of effectiveness (strength of evidence) of treatment vs comparator		
Physical health overall	Favors acupuncture (Insufficient)	Favors CPAP (Low)
Pain	Favors acupuncture (Insufficient)	Favors CPAP (Low)
Cognitive	---	Favors CPAP (Low)
Fatigue	---	Favors CPAP (Low)
Mental health overall	---	Favors CPAP (Low)
Depression	---	---
Global outcomes (function, QoL)	---	---

PTSD symptoms	---	---
Sleep	---	Favors CPAP (Low)
GI symptoms	---	---
Adverse events	Unclear (Insufficient)	---

Abbreviations: CBT=Cognitive Behavioral Therapy; GI=Gastrointestinal; MBB=Mind-body Bridging; MBSR=Mindfulness-based Stress Reduction; N=Number of Participants; PTSD=Posttraumatic Stress Disorder; QoL=Quality of Life; ROB=Risk of Bias; SOE=Strength of Evidence

KEY QUESTION 2: Do the effectiveness or harms of the interventions/strategies differ among subgroups of Veterans with GWI, such as female Veterans or cases defined by specific criteria, in comparison with Veterans with GWI overall?

We found no studies that compared the effects of an intervention in a subpopulation with a broader sample of GWI patients. Four studies included in KQ1 limited their inclusion criteria to specific symptoms or subpopulations (IBS in a study of rifaximin,[4] sleep-disordered breathing in a study of CPAP,[12] sleep disturbance in a study of mind-body bridging,[10] and patients positive for mycoplasma DNA in a study of doxycycline[1]). Although the findings of these studies may be most applicable to the targeted subpopulations, we are not able to draw conclusions about whether the treatments affect symptoms differently in these subpopulations compared with GWI patients overall.

KEY QUESTION 3: What interventions for GWI have been examined in noncomparative studies and ongoing/unpublished trials or cohort studies?

Summary of Findings

We found 31 ongoing or unpublished trials and 2 published noncomparative intervention studies. Although 2 of the clinical trials were terminated before completion, we have included them in the characterization of current research in this area so that future researchers are aware of what interventions have been attempted. A brief list of the interventions, comparators, projected sample sizes, and targeted symptom or subpopulations are shown in Table 7. Detailed information about each study is provided in Appendix D, Table 13.

We identified 33 ongoing, single-arm pilot, or unpublished studies of treatments for GWI symptoms in the following areas: behavioral and psychological interventions (4), various forms of central nervous system stimulation devices (5), complimentary and integrated health interventions including movement therapies (4), dietary interventions (2), exercise (1), medications (7), nutritional supplements (7), stochastic noise electrical stimulation (1), nasal irrigation (1), and light-emitting diode (LED) therapy (1). These represent a much broader range of interventions than completed trials included in our question about effectiveness (KQ1) with only a few treatments that have been tested in earlier trials: 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 (See Appendix D, Table 13).

Because many of these studies are ongoing, we were not able to rate the ROB for the individual studies or draw conclusions. Four RCTs have made results publicly available, although 3 did not report between-group statistical analyses. Preliminary results (N=17) from 1 crossover RCT of a low-glutamate diet found significant improvement in PTSD and anxiety (see Appendix D, Table 15).[25]

Two additional single-arm pilot studies also showed a pre-post treatment effect, but these results would need to be replicated in a larger sample and may suggest future areas of research (see Appendix D, Table 16).

Table 7. Interventions for GWI in ongoing/unpublished clinical trials and single-arm studies

Intervention category	Treatment	Comparator	Sample size*	Targeted symptom or subpopulation	Status
Behavioral	CBT[26]	Waitlist	80	Insomnia	Ongoing
	Cognitive rehabilitation[27]	Health education	268	---	Completed, no results posted
	Mindfulness-Based Stress Reduction[28]	Adapted CDSMP	308	---	Ongoing
Behavioral, multicomponent	Specialized Care Program[29]	No comparator	109	---	Published
CNS stimulation	(HD) tDCS[30]	Sham HD tDCS	120	---	Ongoing
	rTMS[23]	Sham rTMS	---	Chronic musculoskeletal pain	Terminated before completion
	rTMS[31]	Sham rTMS	90	Migraines, and muscle/ joint pain	Ongoing
	rTMS[32]	Sham rTMS	80	Migraines, muscle/ joint pain, and depression	Ongoing
	rTMS[33]	Sham rTMS	150	Headaches and pain	Ongoing
	tDCS[34]	Sham tDCS	120	---	Ongoing
	VNS[35]	Placebo	40	Widespread pain and migraines	Ongoing
Complementary and integrative health	Acupressure[36]	Reiki	7	Pain and fatigue	Completed, no results posted
	Meditation + acupuncture[37]	GW Health education	172	---	Ongoing
	Tai Chi[38]	Wellness intervention (video and mindfulness)	120	Joint pain/stiffness	Ongoing
	Yoga[39]	CBT	75	Chronic pain	Completed, results posted
Diet	Low-FODMAP diet[40]	High-FODMAP diet	68	IBS	Completed, no results posted
	Low-glutamate diet[41,42]	Waitlist	40	---	Ongoing

Intervention category	Treatment	Comparator	Sample size*	Targeted symptom or subpopulation	Status
Exercise	Exercise training[43]	Waitlist	77	Chronic musculoskeletal pain	Completed, no results posted
Medication	D-cycloserine[44]	Placebo	56	Cognitive symptoms	Ongoing
	Duloxetine vs pregabalin[24]	Placebo	---	Pain	Terminated before completion
	Etanercept+ mifepristone[45]	No comparator	20	Safety	Ongoing
	Intranasal insulin[46]	Placebo	114	Cognitive symptoms	Ongoing
	Prednisone[47]	Placebo	100	---	Ongoing
	Pregnenolone[48]	Placebo	170	---	Completed, no results posted
	Rituximab[49]	Placebo	NR	---	Ongoing
Medication + nutritional supplement	Nutrient formula + methylphenidate[50]	No comparator	15	---	Published
Nutritional supplement	Botanical Microglia Modulators[51]	Placebo	64	---	Ongoing
	Concord grape juice[52]	Placebo	36	---	Completed, no results posted
	Mitochondrial cocktail[53]	Placebo	NR	---	Ongoing
	Resveratrol[54]	Placebo	68	---	Ongoing
	Ubiquinol (CoQ10)[55]	Placebo	200	---	Ongoing
	Visbiome vs VSL#3[56]	Placebo	60	IBS	Ongoing
Other	Electrical stimulation (stochastic noise)[57]	Sham electrical stimulation	60	Vestibular function; postural sway	Completed; unpublished
	LED therapy[58]	Sham LED	160	Neuropsychological symptoms	Ongoing
	Nasal irrigation (Xylitol)[59,60]	Saline NI; Usual care	40	Chronic rhinosinusitis	Completed, results posted

*projected sample size, actual size may differ
Abbreviations: CDSMP=Chronic Disease Self-Management Program; CN =Central Nervous System; CoQ10=Coenzyme Q_{10}; FODMAP=Fermentable Oligo-, Di-, Mono-saccharides and Polyols; GW=Gulf War; HD tDCS=High Definition Transcranial Direct Current Stimulation; LED=Light-emitting Diodes; NI=Nasal Irrigation; NR=Not Reported; rTMS=Repetitive Transcranial Magnetic Stimulation; tDCS=Transcranial Direct Current Stimulation; VNS=Vagus Nerve Stimulation; VSL=Very Safe Lactobacilli

Ongoing and Unpublished Studies – Detailed Findings

Behavioral interventions

Two randomized controlled trials (1 in progress[26] and 1 unpublished but completed[27]) are testing CBT for GWI. The ongoing study[26] is testing telephone-delivered, insomnia-focused CBT for Veterans with GWI and insomnia compared to usual care, and the other trial tested problem-solving therapy for cognitive rehabilitation compared to health education in GWI Veterans.[27] A third, ongoing behavioral study is comparing MBSR to a Chronic Disease Self-Management Program (CDSMP) in Veterans with CMI.[28] A subset of the study population will be Gulf War Veterans. No results are available yet for these studies (Appendix D, Table 13).

Brain stimulation therapy

Six RCTs are testing brain stimulation therapies (Appendix D, Table 13).[30-35] Three studies are examining rTMS versus sham rTMS, 2 are investigating tDCS versus sham tDCS,[30,34] and 1 is studying vagus nerve stimulation (VNS) versus sham VNS.[35] Three of the 6 trials required participants have migraines in addition to GWI in their inclusion criteria.[31,32,35] One additional study of rTMS was terminated due to low enrollment.[23] Results have not been reported for any of these RCTs.

Complementary and integrative health (CIH)

Four trials examined CIH interventions (Appendix D, Table 13).[36-39] One nRCT of acupressure versus reiki for GWI-related fatigue and pain[36] was completed in 2017, but has not posted results; an ongoing RCT is examining Tai Chi compared to a wellness intervention for pain and other GWI symptoms[38]; and 1 ongoing RCT is studying meditation (iRest Yoga Nidra) with auricular acupuncture compared to a GW health education control for improving sleep quality in Veterans with GWI.[37]

The fourth study is an RCT completed in early 2018 comparing yoga to CBT for pain in Veterans with GWI.[39,61] This trial reported results for change in within-group mean pain scores measured by the Brief Pain Inventory-Short Form (BPI-SF) from baseline to end of treatment and found that the yoga group improved significantly ($P < 0.001$), but the CBT group did not ($P > 0.05$).[39,62] At 6-month follow-up the yoga group still had significantly improved pain scores compared to baseline ($P = 0.02$), while CBT mean change scores were not reported.[39,62] No between-groups analysis was reported (Results in Appendix D, Table 15).

Diet

Two RCTs are examining the effects of dietary interventions on Veterans with GWI (Appendix D, Table 13).[40,41] One study, that was estimated to have been completed in 2018, compared a low-FODMAP (Fermentable Oligo-, Di-, Mono-saccharides And Polyols) diet to a typical healthy (high-FODMAP) diet for IBS in GW Veterans, but results are not yet reported.[40]

The other dietary RCT is a crossover study examining a low-glutamate diet and subsequent monosodium glutamate (MSG) challenge.[41] This trial is ongoing but has reported some preliminary results for 17 participants.[25,41] The outcomes analyzed were PTSD symptoms measured by the PTSD Checklist – Civilian version (PCL-C) and anxiety measured by the

Generalized Anxiety Disorder 7-item scale (GAD-7). Median scores were reduced significantly over 1-month intervention (PCL-C score P = 0.04; GAD-7 score P = 0.01; Appendix D, Table 15).

Electrical stimulation

In 1 trial, the investigators developed a novel portable electrical stimulation device that provides random, imperceptible stochastic noise via ear clips, intended to improve vestibular function (Appendix D, Table 13).[57,63] Worn constantly during the 12-week trial, it improved ocular torsion (OT) and sway compared to a sham stimulator (Appendix D, Table 15).[57,63]

Exercise

One RCT tested 16 weeks of resistance exercise training compared to a waitlist control for physical symptoms including chronic pain in Veterans with GWI.[43] Completed at the end of 2018, results of the trial are not yet available.

Light-Emitting Diodes therapy

One crossover RCT is comparing a course of LED treatment to sham LED treatment for cognitive symptoms in GWI Veterans (Appendix D, Table 13).[58] The study is ongoing.

Medications

Seven RCTs examined pharmacological interventions for Veterans with GWI symptoms (Appendix D, Table 13).[24,44-49] One RCT studying adjunctive pregnenolone for fatigue, musculoskeletal pain, and cognitive decline in GW veterans[48] was completed in 2018, but has not posted results; 1 small Phase I trial of the combination of etanercept and mifepristone is testing 2 doses of mifepristone (300mg and 600mg) and the primary outcome is safety[45]; 1 RCT, estimated to have been completed in 2017, examined whether intranasal insulin improves cognitive function and other CMI symptoms in GW veterans with CMI[46]; an ongoing RCT of treatment with delayed-release prednisone seeks to determine if it improves the health-related QoL of Veterans with GWI[47]; 1 ongoing RCT is investigating the efficacy of d-cycloserine treatment for GWI[44]; and 1 ongoing RCT is evaluating GWI symptom improvement with the use of b-cell depletion therapy with rituximab.[49] One RCT was testing the treatments of duloxetine and pregabalin for Veterans with GWI, but the study was terminated by the funder in 2019, and no reason was given.[24]

Nasal irrigation

One RCT examined the effectiveness of nasal irrigation with either xylitol or saline versus placebo for chronic rhinosinusitis (CRS) in Veterans with GWI (Appendix D, Table 13).[60] Changes from baseline in fatigue (measured by the Multidimensional Fatigue Inventory [MFI]) and respiratory scores (measured by the 20-item Sinonasal Outcome Test [SNOT-20]) were reported for the 40 participants at weeks 8 and 26 of treatment, but no statistical analyses were presented (Appendix D, Table 15).[59]

Nutritional supplements

Six recent trials examined the effects of nutritional supplements on veterans experiencing GWI symptoms (Appendix D, Table 13).[51-56] One RCT tested the consumption of Concord grape juice for treating cognitive deficits and chronic fatigue in Veterans with GWI[52] was completed in 2019, but has not posted results; 1 controlled trial estimated to have been completed in 2019 examined the benefit of a mitochondrial supplement with an individualized correction or citric acid cycle (CAC) intermediates and amino acid (AA) abnormalities as part of a mitochondrial/oxidative stress treatment approach in GWI[53]; 1 RCT estimated to have been completed in 2018 examined Visbiome and its effects on IBS and non-intestinal symptoms such as fatigue, joint pain, insomnia, general stiffness and headache, associated with IBS[56]; 1 ongoing RCT is using resveratrol as a treatment to improve memory issues, difficulties with thinking and mood problems in Veterans with GWI[54]; 1 ongoing RCT is determining the use of ubiquinol and its effectiveness to improve the physical function in Veterans with GWI[55]; and 1 ongoing crossover RCT is examining various botanical compounds and their effectiveness in suppressing symptoms of GWI.[51]

Single-arm Studies with Published Results

Two published single-arm pre-post studies of interventions for GWI were identified in our search (Appendix D, Tables 14 and 16).[29,50] First, in a specialized care program (SCP) of 109 Veterans, improvements were seen on global physical health outcomes that were maintained at 3-month follow-up.[29] The program was a 3-week intensive outpatient group program that included the development of an individualized symptom-management plan that combined regular primary medical care, exercise, self-care, and other active coping strategies.[29]

The other single-arm study was of 15 Veterans with GWI treated with a nutrient formula and methylphenidate for 12 weeks.[50] Participants improved on measures of fatigue, sleep, cognitive symptoms, and an assessment of GWI symptoms overall, but the small size and lack of comparison group precludes drawing any conclusions from results.

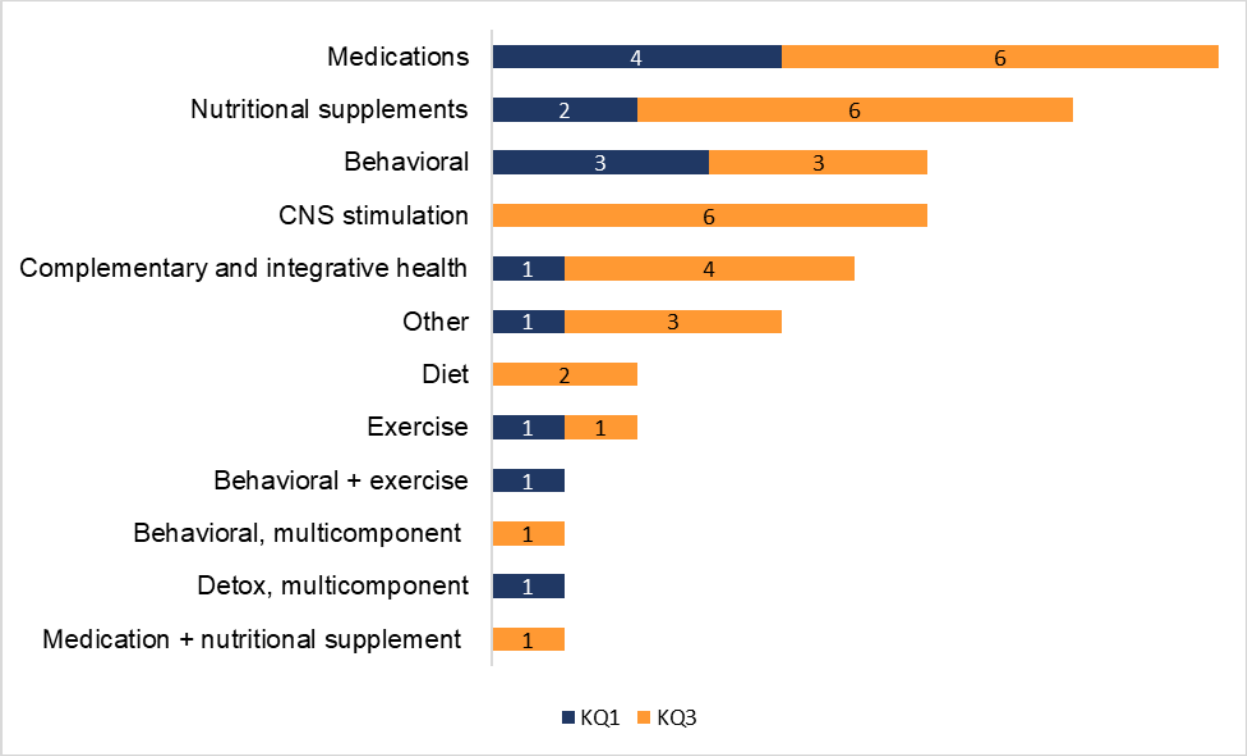
DISCUSSION

We conducted a comprehensive review of treatments for GWI and found studies of several interventions that reported improvements in various GWI symptom domains. A large multi-arm study of CBT and exercise found moderate-strength evidence of benefit with CBT and exercise alone and in combination.[7] Studies of mindfulness-based interventions (MBB and MBSR) also found low-strength evidence of improvement on several outcome measures.[9,10] CPAP improved overall physical health, pain, cognitive functioning, fatigue, mental health, and sleep quality in participants with GWI and sleep-disordered breathing (low SOE).[12] Studies of nutritional supplements[5,6] and acupuncture[11] showed some indications of benefit, though the evidence was insufficient due to methodological issues (Appendix C). Several interventions were found to have no treatment effect, including doxycycline, mifepristone, and naltrexone.

Several trials found promising effects on some outcomes but no treatment effects on other outcome measures. Among the interventions, it is important to also consider potential for harms. Adverse events occurred more frequently with 2 interventions: doxycycline[1] and a detoxification and sauna regimen.[8] It is unclear whether the psychosocial and exercise interventions are associated with increased risk of adverse events. This will be important information to ascertain with greater certainty in future, larger trials.

Among the ongoing studies, there appears to be emerging interest in central nervous system (CNS) stimulation therapies and complementary and integrative health (CIH) approaches for treating GWI. Medications and nutritional supplements continue to be evaluated, although no particular medication has been studied in more than 1 trial in either KQ1 or KQ3. Figure 3 shows the types of interventions examined among the 12 published RCTs in KQ1 and the 32 ongoing/unpublished/single-arm studies in KQ3.

Figure 3. Frequency of intervention categories* among published (KQ1) and unpublished (KQ3) studies of treatments for GWI



*Because 1 study had 3 active treatment arms,[7] there are 47 intervention arms represented among 45 total studies.
Abbreviations: CNS=Central Nervous System; KQ=Key Question.

It has been almost 7 years since the Institute of Medicine's (IOM) *Committee on Gulf War and Health: Treatment for Chronic Multisymptom Illness'* review, which also included studies in non-Veterans and treatments for conditions and comorbidities other than GWI (*eg*, fibromyalgia, IBS, depression, etc.). The IOM report did not conclusively recommend any interventions but advised that antidepressant medications (SSRIs and SNRIs) as well as CBT may be helpful for some. Authors of the report also emphasized that this is a complex illness and individualized health care management plans are necessary. More recently, a narrative review of intervention-focused GWI research was published in 2019,[17] which included 7 studies that also met our inclusion criteria for this review. We have added to the findings of that 2019 review by performing a critical appraisal of the 7 included studies and identifying 5 additional treatment studies. We further conducted a comprehensive search for VA- and DoD-funded studies and found many studies that are ongoing or completed but unpublished. The expanded scope of this review helps to characterize what is currently known about GWI interventions, and to inform future directions for GWI research.

LIMITATIONS

There are several limitations that should be considered, both of our review, as well as of the body of literature that we reviewed. Regarding our review, we were not able to combine results into a meta-analysis due to the heterogeneity of outcomes and interventions assessed.

With regard to the body of literature, there are several limitations to this evidence base. The absence of participant blinding was a frequent limitation, particularly among the psychosocial interventions, which results in potential bias for self-reported outcomes. The magnitude of treatment effect was not always reported, and documentation of adverse events was inconsistent among the trials. Of all the GWI treatment studies we reviewed, only 2 are low ROB (Doxycycline[1] and CPAP[12]) and 1 of them had a very small sample size (CPAP, N=18).[12] Moreover, while CPAP is an evidence-based treatment for sleep apnea, it was also associated with improvement on a broader range of GWI symptom in this study, not just sleep outcomes, so it is important to include.

Heterogeneity

Heterogeneity among the interventions, outcome measures, and other study characteristics limited our ability to draw conclusions. Because we identified only 1 study each of the 12 different interventions included in KQ1, we were unable to conduct meta-analyses.

There are many methodologic challenges in studying treatments for GWI all of which drive the issues of heterogeneity. These include variation in case definition, lack of common and disease-specific outcome measures for GWI, as well as differing interpretations of the pathophysiology of GWI itself. With regard to variation in case definitions, it is a major challenge to develop an evidence base for treating an illness that does not yet have an agreed upon set of symptoms, clinical presentation or measurement tools.[63] While there is overlap in some of the symptoms required to meet either the CDC or Kansas case definitions, individuals with GWI often present with wide range and variability in their symptoms, potentially resulting in too heterogeneous of a sample to see a treatment effect. Luckily 2 ongoing studies both leveraging VA administrative data (one employing a comprehensive chart review; PI: Helmer) and the other is employing a machine learning approach to identify health care data clusters that are associated with GWI (PI: Dursa), both will provide additional clarity on a case definition. Finally, there is a range of illness severity that is not well captured by the current measurement of GWI and not consistently measured and/or reported across the studies. Lack of a standard measure of global GWI symptoms and symptom clusters to measure a potential global reduction also resulted in a high degree of heterogeneity in outcome measures across studies (can cite McNeil 2013 again here). To try and address this challenge, in 2018, the Gulf War Illness Common Data Elements Symptoms Work Group[64] developed a recommendation for the battery of measures to be used to assess symptom frequency, severity, and functional impairment.[65] Ideally, moving forward, trials could use these recommended measures in order to combine results into larger meta-data from which to draw stronger conclusions about effectiveness of treatments.

A common limitation of the psychosocial and exercise intervention literatures was the use of self-reported outcomes accompanied with a lack of participant blinding. The role and necessity of patient blinding in studies of these types of interventions has been debated. There are techniques even for complex nonpharmacologic interventions to blind patients to some degree.[66] Some argue that lack of patient blinding in trials of non-pharmacologic therapies may considerably exaggerate treatment effects.[67] In which case, it would be difficult to determine whether and to what extent positive treatment effects – especially for the findings with only low level confidence – were due to an independent effect of treatment, expectancy as a mechanism of change, placebo effect, or a combination of these factors. On the other hand, others have argued

that blinding is not only challenging but also potentially counterproductive as expectancy for change is thought to be an integral part of the intervention itself.[68]

Publication Bias

For KQ3, we identified lists of funded trials from the DoD[69] and VA and searched for publications based on these funded trials. We found 31 studies that have not been published. Results of 3 of these studies have been posted publicly. No findings have been posted for 5 studies, of which 2 were completed in 2017, and 2 in 2018. The absence of published findings from completed studies suggests the potential for publication bias or other barrier to publication.

Applicability of Findings to the VA Population

All of these studies were conducted in Veteran participants with GWI, and many of the studies that showed effectiveness were conducted in a VA setting, so there is a high degree of applicability to Veterans who receive care at the VA. Also, some of the studies include important subpopulations (*eg*, those with sleep-disordered breathing, PTSD, or IBS). Yet, there may be less applicability to Veterans who do not receive care in the VA or who do not have access to specialty medical, post-deployment, or mental health care.

IMPLICATIONS FOR VHA

The findings of this report can help to inform priorities for future funding and clinical inquiry. There are several promising interventions including mindfulness-based approaches, CBT and exercise (separately or together), and the use of a CPAP among those with sleep-disordered breathing and GWI. The VA is in a unique position to offer integrated specialty and mental health care, which may be the ideal care model to effectively manage those with GWI.

RESEARCH GAPS/FUTURE RESEARCH

There are many areas of future inquiry that should be considered. Several potentially promising interventions that have demonstrated effectiveness to improve 1 or more symptoms include: mindfulness-based approaches, CBT and exercise (separate or together), and the use of a CPAP among those with GWI who have sleep-disordered breathing. The implementation of these in VA should be studied. We identified a broader literature of ongoing or single-arm studies from which we could not draw conclusions, but which may point us in the direction of promising novel therapies. Notable among these was a Specialized Care Program, and dietary interventions (low-glutamate diet; nutrient formula combined with methylphenidate), which warrant further investigation and movement to effectiveness trials.

In the context of an aging population of Gulf War Era Veterans, especially those with GWI, symptoms may be exacerbated either by the aging process or by the development of other medical comorbidities. Interventions with low risk of adverse effects are an important consideration. Studies examining GWI sub-populations were quite limited. Only 3 trials examined effects on Veterans with GWI who also had a specific comorbidity (1 each of IBS, PTSD, and sleep-disordered breathing), leaving many subpopulations in need of future research.

In sum, research gaps and future ways to improve the evidence base include:

(1) Consolidation of intervention work, replicating promising interventions and conducting studies of a hybrid design to assess effectiveness and feasibility of implementation of promising interventions in VA settings;

(2) Development of a single case definition that considers the onset of other chronic health conditions in this aging population;

(3) Development and use of consistent outcome measures capable of assessing the depth and breadth of GWI symptoms, considering the severity of illness to differentiate those with severe and less severe disease, and measuring longitudinal change in symptom severity.

CONCLUSIONS

We found a small but growing body of evidence examining a disparate array of treatments for Veterans with GWI (see Summary Table). 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.

Summary Table. Visual representation of findings

Treatment *Subpopulation if applicable*	**Outcome domain**										
	Physical health overall	**Pain**	**Cognitive**	**Fatigue**	**Mental health overall**	**Depression**	**Global outcomes (function, QoL)**	**PTSD symptoms**	**Sleep**	**GI symptoms**	**Adverse events**
Medications vs placebo											
Doxycycline[1] *Positive mycoplasma*	★★	★★	★★	★★	★★	---	---	---	---	---	★★
Mifepristone[2]	Ø	---	Ø	Ø	Ø	Ø	---	Ø	---	---	Ø
Naltrexone[3]	Ø	---	Ø	---	---	---	---	---	---	---	Ø
Rifaximin[4] *IBS (Rome III)*	---	---	---	---	---	---	Ø	---	---	Ø	Ø
Nutritional supplements vs placebo											
Carnosine[5]	---	Ø	Ø	Ø	---	---	---	---	---	Ø	Ø
CoQ10[6]	Ø	---	Ø	---	---	---	---	---	---	---	Ø
Psychological, exercise, or multi-component interventions											
CBT[a7]	★★	★★	★★	★★	★★	---	---	---	---	---	Ø
Exercise[a7]	★★	★★	★★	★★	★★	---	---	---	---	---	Ø

Treatment *Subpopulation if applicable*	**Outcome domain**										
	Physical health overall	**Pain**	**Cognitive**	**Fatigue**	**Mental health overall**	**Depression**	**Global outcomes (function, QoL)**	**PTSD symptoms**	**Sleep**	**GI symptoms**	**Adverse events**
CBT + Exercise in combination[a7]	★★	★★	★★	★★	★★	---	---	---	---	---	Ø
Detox regimen[b8]	Ø	Ø	---	Ø	Ø	---	Ø	---	---	---	Ø
Mindfulness-based stress reduction[b9]	---	★	★	★	---	★	---	★	---	---	---
Sleep focused mind-body bridging[c10]	Ø	Ø	Ø	★	Ø	★	Ø	★	★	---	---
Other interventions											
Acupuncture[a11]	Ø	Ø	---	---	---	---	---	---	---	---	Ø
CPAP[d12]	★	★	★	★	★	---	---	---	★	---	---

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

[a] Versus usual care/TAU

[b] Versus waitlist

[c] Versus sleep education

[d] Versus sham CPAP

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APPENDIX A. SEARCH STRATEGIES

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 16, 2019

Date searched: September 17, 2019

#	Searches	Results
1	Persian Gulf Syndrome/ or Gulf War/	1069
2	(("Desert Shield" or "Desert Storm" or "Gulf War" or "Gulf Conflict" or "Gulf Crisis" or "Kuwait War" or "Operation GRANBY" or "Op GRANBY") adj7 (bioassay* or bio-assay* or biomarker* or bio-marker* or CFS or (chronic adj (fatigue or headache* or pain or "physical symptom*" or multisymptom or multi-symptom or multisystem or multi-system)) or cluster or cognit* or deployment or detect* or diagnos* or disease* or disorder* or expos* or fibromyalgi* or "functional somatic syndrome*" or gastrointestinal or gastro-intestinal or headache* or identif* or illness or "irritable bowel syndrome*" or ME?CFS or "medically unexplained" or "multiple chemical sensitivit*" or musculoskeletal or musculo-skeletal or myalgi* or neurocognit* or neuro-cognit* or neuropsych* or neuro-psych* or ((nonspecific or non-specific) adj ("chest pain*" or symptom*)) or psychosomatic or pulmonar* or respirator* or sickness or syndrome or somatization or somatoform or temporomandibular or temporo-mandibular or therap* or treat* or war-related)).ti,ab,kf.	1044
3	("Desert Shield" or "Desert Storm" or "Gulf War" or "Gulf Conflict" or "Gulf Crisis" or "Kuwait War" or "Operation GRANBY" or "Op GRANBY").ti,ab,kf. and (di or dg or dt or rt or rh or su or tu or th).fs.	583
4	(GWI or GWIs or GWVI or GWVIs or "Iowa Persian Gulf Study" or "War Related Illness and Injury Study Center*").ti,ab,kf.	200
5	(((Kuwait or Iraq or "Persian Gulf" or "Southwest Asia" or "SW Asia") adj7 ("air force" or "armed forces" or army or marines or "military personnel" or "national guard*" or naval or navy or "service members" or servicemembers or soldier* or veteran*)) and (bioassay* or bio-assay* or biomarker* or bio-marker* or CFS or (chronic adj (fatigue or headache* or pain or "physical symptom*" or multisymptom or multi-symptom or multisystem or multi-system)) or cluster or cognit* or deployment or detect* or diagnos* or disease* or disorder* or expos* or fibromyalgi* or "functional somatic syndrome*" or gastrointestinal or gastro-intestinal or headache* or identif* or illness or "irritable bowel syndrome*" or ME?CFS or "medically unexplained" or "multiple chemical sensitivit*" or musculoskeletal or musculo-skeletal or myalgi* or neurocognit* or neuro-cognit* or neuropsych* or neuro-psych* or ((nonspecific or non-specific) adj ("chest pain*" or symptom*)) or psychosomatic or pulmonar* or respirator* or sickness or syndrome or somatization or somatoform or temporomandibular or temporo-mandibular or therap* or treat* or war-related)).ti,ab,kf.	1566
6	or/1-5	3087
7	6 not ("Enduring Freedom" or "Iran-Iraq" or "Iraq-Iran" or (Iraq adj2 Afghanistan) or "Iraqi Freedom" or OEF or OIF or "Op TELIC" or "Operation TELIC").ti,ab,kf.	1972
8	7 not ((exp animals/ not humans/) or (cat or cats or dog or dogs or mice or mouse or rat or rats or rodent).ti.)	1849
9	limit 8 to english language	1809
10	limit 9 to yr="1990 -Current"	1806

EBM Reviews: Cochrane Central Register of Controlled Trials August 2019
Cochrane Database of Systematic Reviews 2005 to September 11, 2019

Date searched: September 17, 2019

#	Searches	Results
1	(("Desert Shield" or "Desert Storm" or "Gulf War" or "Gulf Conflict" or "Gulf Crisis" or "Kuwait War" or "Operation GRANBY" or "Op GRANBY") adj7 (bioassay* or bio-assay* or biomarker* or bio-marker* or CFS or (chronic adj (fatigue or headache* or pain or "physical symptom*" or multisymptom or multi-symptom or multisystem or multi-system)) or cluster or cognit* or deployment or detect* or diagnos* or disease* or disorder* or expos* or fibromyalgi* or "functional somatic syndrome*" or gastrointestinal or gastro-intestinal or headache* or identif* or illness or "irritable bowel syndrome*" or ME?CFS or "medically unexplained" or "multiple chemical sensitivit*" or musculoskeletal or musculo-skeletal or myalgi* or neurocognit* or neuro-cognit* or neuropsych* or neuro-psych* or ((nonspecific or non-specific) adj ("chest pain*" or symptom*)) or psychosomatic or pulmonar* or respirator* or sickness or syndrome or somatization or somatoform or temporomandibular or temporo-mandibular or therap* or treat* or war-related)).ti,ab.	81
2	("Desert Shield" or "Desert Storm" or "Gulf War" or "Gulf Conflict" or "Gulf Crisis" or "Kuwait War" or "Operation GRANBY" or "Op GRANBY").ti,ab.	97
3	(GWI or GWIs or GWVI or GWVIs or "Iowa Persian Gulf Study" or "War Related Illness and Injury Study Center*").ti,ab.	45
4	(((Kuwait or Iraq or "Persian Gulf" or "Southwest Asia" or "SW Asia") adj7 ("air force" or "armed forces" or army or marines or "military personnel" or "national guard*" or naval or navy or "service members" or servicemembers or soldier* or veteran*)) and (bioassay* or bio-assay* or biomarker* or bio-marker* or CFS or (chronic adj (fatigue or headache* or pain or "physical symptom*" or multisymptom or multi-symptom or multisystem or multi-system)) or cluster or cognit* or deployment or detect* or diagnos* or disease* or disorder* or expos* or fibromyalgi* or "functional somatic syndrome*" or gastrointestinal or gastro-intestinal or headache* or identif* or illness or "irritable bowel syndrome*" or ME?CFS or "medically unexplained" or "multiple chemical sensitivit*" or musculoskeletal or musculo-skeletal or myalgi* or neurocognit* or neuro-cognit* or neuropsych* or neuro-psych* or ((nonspecific or non-specific) adj ("chest pain*" or symptom*)) or psychosomatic or pulmonar* or respirator* or sickness or syndrome or somatization or somatoform or temporomandibular or temporo-mandibular or therap* or treat* or war-related)).ti,ab.	173
5	or/1-4	264
6	5 not ("Enduring Freedom" or "Iran-Iraq" or "Iraq-Iran" or (Iraq adj2 Afghanistan) or "Iraqi Freedom" or OEF or OIF or "Op TELIC" or "Operation TELIC").ti,ab.	117

PsycINFO 1806 to September Week 2 2019

Date searched: September 17, 2019

#	Searches	Results
1	(("Desert Shield" or "Desert Storm" or "Gulf War" or "Gulf Conflict" or "Gulf Crisis" or "Kuwait War" or "Operation GRANBY" or "Op GRANBY") adj7 (bioassay* or bio-assay* or biomarker* or bio-marker* or CFS or (chronic adj (fatigue or headache* or pain or "physical symptom*" or multisymptom or multi-symptom or multisystem or multi-system)) or cluster or cognit* or deployment or detect* or diagnos* or disease* or disorder* or expos* or fibromyalgi* or "functional somatic syndrome*" or gastrointestinal or gastro-intestinal or headache* or identif* or illness or "irritable bowel syndrome*" or ME?CFS or "medically unexplained" or "multiple chemical sensitivit*" or musculoskeletal or musculo-	375

	skeletal or myalgi* or neurocognit* or neuro-cognit* or neuropsych* or neuro-psych* or ((nonspecific or non-specific) adj ("chest pain*" or symptom*)) or psychosomatic or pulmonar* or respirator* or sickness or syndrome or somatization or somatoform or temporomandibular or temporo-mandibular or therap* or treat* or war-related)).ti,ab.	
2	("Desert Shield" or "Desert Storm" or "Gulf War" or "Gulf Conflict" or "Gulf Crisis" or "Kuwait War" or "Operation GRANBY" or "Op GRANBY").ti,ab.	1122
3	(GWI or GWIs or GWVI or GWVIs or "Iowa Persian Gulf Study" or "War Related Illness and Injury Study Center*").ti,ab.	57
4	(((Kuwait or Iraq or "Persian Gulf" or "Southwest Asia" or "SW Asia") adj7 ("air force" or "armed forces" or army or marines or "military personnel" or "national guard*" or naval or navy or "service members" or servicemembers or soldier* or veteran*)) and (bioassay* or bio-assay* or biomarker* or bio-marker* or CFS or (chronic adj (fatigue or headache* or pain or "physical symptom*" or multisymptom or multi-symptom or multisystem or multi-system)) or cluster or cognit* or deployment or detect* or diagnos* or disease* or disorder* or expos* or fibromyalgi* or "functional somatic syndrome*" or gastrointestinal or gastro-intestinal or headache* or identif* or illness or "irritable bowel syndrome*" or ME?CFS or "medically unexplained" or "multiple chemical sensitivit*" or musculoskeletal or musculo-skeletal or myalgi* or neurocognit* or neuro-cognit* or neuropsych* or neuro-psych* or ((nonspecific or non-specific) adj ("chest pain*" or symptom*)) or psychosomatic or pulmonar* or respirator* or sickness or syndrome or somatization or somatoform or temporomandibular or temporo-mandibular or therap* or treat* or war-related)).ti,ab.	1314
5	or/1-4	2310
6	5 not ("Enduring Freedom" or "Iran-Iraq" or "Iraq-Iran" or (Iraq adj2 Afghanistan) or "Iraqi Freedom" or OEF or OIF or "Op TELIC" or "Operation TELIC").ti,ab.	1318
7	6 not ((exp animals/ not humans/) or (cat or cats or dog or dogs or mice or mouse or rat or rats or rodent).ti.)	1291
8	limit 7 to english language	1243
9	limit 8 to yr="1990 -Current"	1242

CINAHL with Full Text

Date searched: September 17, 2019

S1	(MH "Persian Gulf Syndrome")	264
S2	TI ((("Desert Shield" or "Desert Storm" or "Gulf War" or "Gulf Conflict" or "Gulf Crisis" or "Kuwait War" or "Operation GRANBY" or "Op GRANBY") N7 (bioassay* or bio-assay* or biomarker* or bio-marker* or CFS or (chronic N1 (fatigue or headache* or pain or "physical symptom*" or multisymptom or multi-symptom or multisystem or multi-system)) or cluster or cognit* or deployment or detect* or diagnos* or disease* or disorder* or expos* or fibromyalgi* or "functional somatic syndrome*" or gastrointestinal or gastro-intestinal or headache* or identif* or illness or "irritable bowel syndrome*" or ME?CFS or "medically unexplained" or "multiple chemical sensitivit*" or musculoskeletal or musculo-skeletal or myalgi* or neurocognit* or neuro-cognit* or neuropsych* or neuro-psych* or ((nonspecific or non-specific) N1 ("chest pain*" or symptom*)) or psychosomatic or pulmonar* or respirator* or sickness or syndrome or somatization or somatoform or temporomandibular or temporo-mandibular or therap* or treat* or war-related))) OR AB ((("Desert Shield" or "Desert Storm" or "Gulf War" or "Gulf Conflict" or "Gulf Crisis" or "Kuwait War" or "Operation GRANBY" or "Op GRANBY") N7 ((bioassay* or bio-assay* or biomarker* or bio-marker* or CFS or (chronic N1 (fatigue or headache* or pain or "physical symptom*" or multisymptom or multi-symptom or multisystem or multi-system))	313

	or cluster or cognit* or deployment or detect* or diagnos* or disease* or disorder* or expos* or fibromyalgi* or "functional somatic syndrome*" or gastrointestinal or gastro-intestinal or headache* or identif* or illness or "irritable bowel syndrome*" or ME?CFS or "medically unexplained" or "multiple chemical sensitivit*" or musculoskeletal or musculo-skeletal or myalgi* or neurocognit* or neuro-cognit* or neuropsych* or neuro-psych* or ((nonspecific or non-specific) N1 ("chest pain*" or symptom*)) or psychosomatic or pulmonar* or respirator* or sickness or syndrome or somatization or somatoform or temporomandibular or temporo-mandibular or therap* or treat* or war-related)))	
S3	TI (("Desert Shield" or "Desert Storm" or "Gulf War" or "Gulf Conflict" or "Gulf Crisis" or "Kuwait War" or "Operation GRANBY" or "Op GRANBY")) OR AB (("Desert Shield" or "Desert Storm" or "Gulf War" or "Gulf Conflict" or "Gulf Crisis" or "Kuwait War" or "Operation GRANBY" or "Op GRANBY"))	629
S4	TI ((GWI or GWIs or GWVI or GWVIs or "Iowa Persian Gulf Study" or "War Related Illness and Injury Study Center*")) OR AB ((GWI or GWIs or GWVI or GWVIs or "Iowa Persian Gulf Study" or "War Related Illness and Injury Study Center*"))	44
S5	TI ((veteran* N15 ("chronic fatigue" or fibromyalg* or "medically unexplained" or multisymptom or multi-symptom or multisystem or multi-system or myalgi* or ME/CFS))) OR AB ((veteran* N15 ("chronic fatigue" or fibromyalg* or "medically unexplained" or multisymptom or multi-symptom or multisystem or multi-system or myalgi* or ME/CFS)))	52
S6	TI ((((Kuwait or Iraq or "Persian Gulf" or "Southwest Asia" or "SW Asia") N7 ("air force" or "armed forces" or army or marines or "military personnel" or "national guard*" or naval or navy or "service members" or servicemembers or soldier* or veteran*)) and (bioassay* or bio-assay* or biomarker* or bio-marker* or CFS or (chronic N1 (fatigue or headache* or pain or "physical symptom*" or multisymptom or multi-symptom or multisystem or multi-system)) or cluster or cognit* or deployment or detect* or diagnos* or disease* or disorder* or expos* or fibromyalgi* or "functional somatic syndrome*" or gastrointestinal or gastro-intestinal or headache* or identif* or illness or "irritable bowel syndrome*" or ME?CFS or "medically unexplained" or "multiple chemical sensitivit*" or musculoskeletal or musculo-skeletal or myalgi* or neurocognit* or neuro-cognit* or neuropsych* or neuro-psych* or ((nonspecific or non-specific) N1 ("chest pain*" or symptom*)) or psychosomatic or pulmonar* or respirator* or sickness or syndrome or somatization or somatoform or temporomandibular or temporo-mandibular or therap* or treat* or war-related))) OR AB ((((Kuwait or Iraq or "Persian Gulf" or "Southwest Asia" or "SW Asia") N7 ("air force" or "armed forces" or army or marines or "military personnel" or "national guard*" or naval or navy or "service members" or servicemembers or soldier* or veteran*)) and (bioassay* or bio-assay* or biomarker* or bio-marker* or CFS or (chronic N1 (fatigue or headache* or pain or "physical symptom*" or multisymptom or multi-symptom or multisystem or multi-system)) or cluster or cognit* or deployment or detect* or diagnos* or disease* or disorder* or expos* or fibromyalgi* or "functional somatic syndrome*" or gastrointestinal or gastro-intestinal or headache* or identif* or illness or "irritable bowel syndrome*" or ME?CFS or "medically unexplained" or "multiple chemical sensitivit*" or musculoskeletal or musculo-skeletal or myalgi* or neurocognit* or neuro-cognit* or neuropsych* or neuro-psych* or ((nonspecific or non-specific) N1 ("chest pain*" or symptom*)) or psychosomatic or pulmonar* or respirator* or sickness or syndrome or somatization or somatoform or temporomandibular or temporo-mandibular or therap* or treat* or war-related)))	804
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	1,434
S8	S7 NOT ("Enduring Freedom" or "Iran-Iraq" or "Iraq-Iran" or (Iraq N2 Afghanistan) or "Iraqi Freedom" or OEF or OIF or "Op TELIC" or "Operation TELIC") **Limiters** –	167

	Published Date: 19900101-20191231; English Language; Exclude MEDLINE records; Human	

Scopus

Date searched: September 17, 2019

TITLE-ABS-KEY ("Desert Shield" OR "Desert Storm" OR "Gulf War" OR "Gulf Conflict" OR "Gulf Crisis" OR "Kuwait War" OR "Operation GRANBY" OR "Op GRANBY" OR "Iowa Persian Gulf Study" OR "War Related Illness and Injury Study Center")
AND DOCTYPE (cp)
AND PUBYEAR > 1989
AND (LIMIT-TO (LANGUAGE , "English"))
= 308 results

Allied and Complementary Medicine (AMED)

Date searched: October 1, 2019

#	Searches	Results
S8	S6 NOT S7 Limiters - Published Date: 19900101-20200131; Language: English	55
S7	TI (cat OR cats OR dog OR dogs OR mice OR mouse OR rat OR rats OR rodent)	7,158
S6	S4 NOT S5	58
S5	TI ("Enduring Freedom" OR "Iran-Iraq" OR "Iraq-Iran" OR (Iraq N2 Afghanistan) OR "Iraqi Freedom" OR OEF OR OIF OR "Op TELIC" OR "Operation TELIC") OR AB ("Enduring Freedom" OR "Iran-Iraq" OR "Iraq-Iran" OR (Iraq N2 Afghanistan) OR "Iraqi Freedom" OR OEF OR OIF OR "Op TELIC" OR "Operation TELIC")	191
S4	S1 OR S2 OR S3	116
S3	TI (((Kuwait OR Iraq OR "Persian Gulf" OR "Southwest Asia" OR "SW Asia") N7 ("air force" OR "armed forces" OR army OR marines OR "military personnel" OR "national guard*" OR naval OR navy OR "service members" OR servicemembers OR soldier* OR veteran*)) AND (bioassay* OR bio-assay* OR biomarker* OR bio-marker* OR CFS OR (chronic N1 (fatigue OR headache* OR pain OR "physical symptom*" OR multisymptom OR multi-symptom OR multisystem OR multi-system)) OR cluster OR cognit* OR deployment OR detect* O ...	74
S2	TI (GWI OR GWIs OR GWVI OR GWVIs OR "Iowa Persian Gulf Study" OR "War Related Illness and Injury Study Center*") OR AB (GWI OR GWIs OR GWVI OR GWVIs OR "Iowa Persian Gulf Study" OR "War Related Illness and Injury Study Center*")	7
S1	TI (("Desert Shield" OR "Desert Storm" OR "Gulf War" OR "Gulf Conflict" OR "Gulf Crisis" OR "Kuwait War" OR "Operation GRANBY" OR "Op GRANBY") N7 (bioassay* OR bio-assay* OR biomarker* OR bio-marker* OR CFS OR (chronic N1 (fatigue OR headache* OR pain OR "physical symptom*" OR multisymptom OR multi-symptom OR multisystem OR multi-system)) OR cluster OR cognit* OR deployment OR detect* OR diagnos* OR	45

	disease* OR disorder* OR expos* OR fibromyalgi* OR "functional somatic syndrome*" OR gastrointest ...	

ClinicalTrials.gov

Date searched: September 17, 2019

OTHER TERMS: "Desert Shield" OR "Desert Storm" OR "Gulf War" OR "Gulf Conflict" OR "Gulf Crisis" OR "Kuwait War" OR "Operation GRANBY" OR "Op GRANBY" OR "Iowa Persian Gulf Study" OR "War Related Illness and Injury Study Center" = 71 results

WHO ICTRP

Date searched: September 17, 2019

TITLE: "Desert Shield" OR "Desert Storm" OR "Gulf War" OR "Gulf Conflict" OR "Gulf Crisis" OR "Kuwait War" OR "Operation GRANBY" OR "Op GRANBY" OR "Iowa Persian Gulf Study" OR "War Related Illness and Injury Study Center" RECRUITMENT STATUS=ALL DATE OF REGISTRATION= 01/01/1990 – 17/09/2019 = 56 results

APPENDIX B. STUDY SELECTION

Inclusion codes, code definitions, and criteria

1. Is the full-text of the article in English?
   Yes → Proceed to 2.
   No → **Code X1** *(Non-English-language publication).* STOP.

2. Does the population include Veterans with Gulf War Illness?
   Include: Veterans (either U.S. or international) deployed to the Persian Gulf region between Aug 2, 1990 - Nov 1991, defined by the authors as having Gulf War Illness according to a recognized case definition (CDC or Kansas), or defines cases using similar criteria to CDC/Kansas, or using illness definitions prior to CDC/Kansas criteria (Chronic Multisymptom/multisystem) Illness (CMI), Irritable Bowel Syndrome (IBS), Chronic Fatigue Syndrome (CFS)/Myalgic Encephalitis (EM), fibromyalgia (FM), Gulf War Syndrome). Also include studies of civilian contractors present during the conflict, if available. Include studies where deployment status and/or time of deployment is unclear.

   Yes → Proceed to 3.
   No → Code **X2** *(Excluded population).* STOP.

3. Does the study examine the benefits and/or harms of an intervention or management strategy (*pharmacological, supplement, non-pharmacological, behavioral, etc. – no exclusions*) for treating symptoms of Gulf War Illness?

   Yes → Proceed to 4.
   No → Is the study about a potential biomarker for GWI?
   Yes → Code **Biomarker.** STOP.
   No → Code **X3** *(Not relevant to GWI interventions or biomarkers).* STOP.

4. Is the study a *published* randomized controlled trial, non-randomized controlled trial, or cohort study that compares the intervention to placebo, usual care, or another active intervention, among Veterans with GWI?

   Yes → Code **Tx-KQ1-[specify intervention, specify condition if subset of GWI].** Proceed to 6.

   No, compares GWI with a non-GWI population → Code **X4** *(non-GWI comparator*). STOP.

   No, it is a systematic review/meta-analysis of GWI interventions → Code **Tx-SR**. STOP.

   No, it is a protocol/abstract/unpublished report that otherwise meets these criteria → Code **Tx-KQ3 emerging research [specify intervention].** STOP.

   No, for none of the reasons above → Proceed to 5.

5. Is the GWI intervention study a single-arm study or case series in which all participants received the same intervention for GWI?
   Yes → Code **Tx-KQ3 single-arm [specify intervention].** STOP.
   No → Code **X5** (*excluded study design or publication type*). STOP.

   Exclude: case studies, editorials, letters, and review articles that are non-systematic.

   Mark "B" any X5's that may contain useful content for background/discussion, eg:
   B-X5 – Narrative review with good background
   B-X5 – May be useful for discussion

6. Does the study examine effectiveness or harms in a subgroup (defined by gender, symptom severity, case definition, or branch of military, as examples) compared with a larger population of Veterans with GWI?
   Yes → **Add code KQ2** (*eg*, Tx-KQ1-KQ2). STOP.
   No → STOP.

Key Questions:

1. Evidence on effectiveness/harms: What are the benefits and harms of pharmacological and non-pharmacological interventions and management strategies for Veterans with GWI?

2. Evidence about subgroups: Do the effectiveness or harms of the interventions/strategies differ among subgroups of Veterans with GWI, such as female Veterans or cases defined by specific criteria, in comparison with Veterans with GWI overall?

3. Emerging research: What interventions for GWI have been examined in
   a) noncomparative studies only?
   b) ongoing/unpublished trials or cohort studies?

Exclusion Codes:
X1: Non-English-language publication
X2: Excluded population
X3: Not relevant to GWI interventions or biomarkers
X4: Non-GWI comparator
X5: Excluded study design or publication type
X9: Duplicate or preliminary publication of a more recent study
X99: Study terminated

APPENDIX C. QUALITY ASSESSMENT CRITERIA

Cochrane Rob 2.0:[20] Five domains through which bias may be introduced	
1. Risk of bias arising from the randomization process: 1.1. Was the allocation sequence random? 1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions? 1.3. Did baseline differences between intervention groups suggest a problem with the randomization process?	
2. Risk of bias due to deviations from the intended interventions (effect of assignment to intervention): 2.1. Were participants aware of their assigned intervention during the trial? 2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? 2.5. If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? 2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention? 2.7. If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	
3. Risk of bias due to missing outcome data: 3.1. Were data for this outcome available for all, or nearly all, participants randomized? 3.2. If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data? 3.3. If N/PN to 3.2: Could missingness in the outcome depend on its true value? 3.4. If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	
4. Risk of bias in measurement of the outcome: 4.1. Was the method of measuring the outcome inappropriate? 4.2. Could measurement or ascertainment of the outcome have differed between intervention groups? 4.3. If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ? 4.4. If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? 4.5. If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	
5. Risk of bias in selection of the reported result: 5.1. Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? Is the numerical result being assessed likely to have been selected, on the basis of the results, from... 5.2. ...multiple outcome measurements (*eg*, scales, definitions, time points) within the outcome domain? 5.3. ...multiple analyses of the data?	
Overall risk-of-bias judgement	
Low ROB	The study is judged to be at **low risk of bias for all domains** for this result.
Some Concerns	The study is judged to raise **some concerns** in at least 1 domain for this result, but not to be at high risk of bias for any domain.
High ROB	The study is judged to be at **high risk of bias** in at least one domain for this result. OR The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

Table 8. Risk of bias in trials of interventions for Gulf War Illness

Experimental intervention	Comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias	Comment
Medications								
Doxycycline[1]	Placebo	Low	Low	Low	Low	Low	Low	---
Mifepristone[2]	Placebo	Low	Low	Low	Some concerns	Low	Some concerns	Analyzed completers only. Statistically underpowered: the intended sample size of 40 not reached due to recruitment difficulties.
Naltrexone[3]	Placebo	Some concerns	Low	Low	High	High	High	Randomization and allocation concealment (cards drawn from box. Analyzed CGIS-responders vs non responders, not by randomization (Tx vs placebo).
Rifaximin[4]	Placebo	Low	Some concerns	Low	Low	Low	Some concerns	Analyzed completers only.
Nutritional supplements								
CoQ10[6]	Placebo	Low	Low	Low	Low	High	High	Post-protocol changes in analytic approach; threshold/magnitude of change not defined for binary analyses of improvement.
Carnosine[5]	Placebo	Low	Some concerns	High	Low	Low	High	Differential loss to follow-up: 37% vs 13.3% Analyzed completers only.
Psychological, exercise, and multi-component interventions								
CBT + Exercise[7]	TAU	Low	Low	Low	Some concerns	Low	Some concerns	Self-reported outcomes, subjects not blinded
Detox regimen[8]	Waitlist	Some concerns	Low	Low	Some concerns	Low	Some concerns	Baseline differences in % disabled vs employed self-reported outcomes, subjects not blinded.
Mindfulness-based therapy[9]	TAU	Low	Low	Low	Some concerns	Low	Some concerns	Self-reported outcomes, subjects not blinded.

Experimental intervention	Comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias	Comment
Sleep-focused Mind-Body Therapy[10]	Sleep education	Low	Low	Low	Some concerns	Low	Some concerns	Self-reported outcomes, subjects not blinded
Other interventions								
Acupuncture (bi-weekly)[11]	Waitlist/ acupuncture (weekly)	Low	Some concerns	Low	Some concerns	Low	Some concerns	Self-reported outcomes; participants and intervention staff not blinded
CPAP[12]	Sham CPAP	Low	Low	Low	Low	Low	Low	---

Abbreviations: CBT=Cognitive Behavioral Therapy; CoQ10=Coenzyme Q10; CPAP=Continuous Positive Airway Pressure; IBS=Irritable Bowel Syndrome; MBB=Mind-body Bridging; MBSR=Mindfulness-based Stress Reduction; QoL=Quality of Life; ROB=Risk of Bias; SF-36=36-Item Short Form Health Survey; Sx=symptom; TAU=Treatment as Usual; Tx=Treatment; WAIS-R=Wechsler Adult Intelligence Scale-Revised.

APPENDIX D. DATA SUPPLEMENT

Table 9. Results for physical health, pain, and fatigue outcomes in intervention trials for Gulf War Illness

Intervention and study characteristics[a]	Physical Health Overall	Pain	Fatigue
Medications			
Doxycycline[1] (n=245) vs placebo (n=246) Total N=491 Subpopulation: positive mycoplasma DNA test Tx duration: 12 months Observation: 18 months ROB: Low	Veterans SF-36 PCS Pt score N analyzed: 199 vs 212 Least-square mean difference (95% CI; Tx minus C) at 12 months: 1.0 (-0.3 to 2.4), P=0.12	McGill Pain Questionnaire (N analyzed), least-square mean difference (95% CI; Tx minus C) at 12 months: Sensory (207 vs 214): -0.6 (-1.8 to 0.6), P > 0.2 Affective (206 vs 214): 0.0 (-0.5 to 0.5), P > 0.2 Pain now (207 vs 213): -0.3 (-0.7 to 0.1), P=0.18 Typical pain (206 vs 213): 0.0 (-0.4 to 0.3), P > 0.2	MFI (N analyzed), least-square mean difference (95% CI; Tx minus C) at 12 months: General fatigue (206 vs 214): -0.1 (-0.7 to 0.5), P > 0.2 Physical fatigue (206 vs 214): -0.1 (-0.6 to 0.5), P > 0.2 Reduced activity (207 vs 214): 0.0 (-0.6 to 0.7), P > 0.2 Reduced motivation (206 vs 214): -0.2 (-0.8 to 0.4), P > 0.2 Mental fatigue (206 vs 213): 0.0 (-0.6 to 0.6), P > 0.2
Mifepristone[2] (n=18 in each phase 1 and 2) vs placebo (n=18 in phase 1, n=15 in phase 2), 6-week crossover phases, 1m washout Phase 1 Total N=36 Phase 2 Total N=33 Tx duration: 6 weeks Observation: 4 months ROB: Some concerns	Veterans SF-36 (acute form) PCS score: Mifepristone treatment was not associated with improvement in self-reported physical health status (p=0.838) Overall mean change, ΔT minus ΔC (SD): -0.46 (7.76), P=0.738	NR	General fatigue (MFI-20) Overall mean change, ΔT minus ΔC (SD): 0.63 (3.37), P=0.302
Naltrexone[3] vs placebo (n's=NR), crossover phases separated by 1-month washout. Total N=40 Tx duration: 3 months Observation: 7 months ROB: High	Change in CGIS favored naltrexone: 14 (35%) Change in CGIS favored placebo: 5 (12.5%) No change from baseline: 18 (45%) (Tx vs C not significant)	NR	NR
Nutritional supplements			

Intervention and study characteristics[a]	Physical Health Overall	Pain	Fatigue
Carnosine[5] (n=12 finished study) vs placebo (n=13 finished study) Total N=34 Tx duration: 12 weeks Observation: 14 weeks ROB: High	NR	No changes in average (dolorimetry) pain thresholds, and no differences between groups.	CFS severity score: no differences between groups. Instantaneous fatigue scores: no treatment effects.
CoQ10[6] 100 mg/d (n=11) vs 300 mg/d (n=12) vs placebo (n=23) Total N=46 Tx duration: 3.5 +/- 0.5 months Observation: 3.5 +/- 0.5 months ROB: High	GSRH: improved from baseline (threshold not defined for improved/not improved): Q100 (N=10) vs placebo (N=19): OR (95% CI): All Pts (N=46): 1.88 (0.26 to 13.4), P=0.53 Physical function assessed by Summary Performance Score: Q100 vs Placebo, % Pts Improved from baseline: 82% vs 40% Absolute difference: 42% (P=0.025). Women contributed to this benefit. Q300 vs Placebo, % Pts Improved from baseline: 55% vs 40% Absolute difference: 15% (P=0.44). SPS improvement on Q300 was not significant, though the effect on Q100 did not differ significantly from that on Q300 (P=0.17).	NR	NR
Psychological, exercise, or multi-component interventions			
CBT+Exercise[7] (n=266) vs CBT (n=286) vs Exercise (n=265) vs TAU (n=270) Total N=1092 Tx duration: 12 weeks Observation: 12 months ROB: Some concerns	VSF-36 PCS Score: % of Pts with 7+ points improvement vs baseline at 3 months, 6 months, 12 months: CBT + exercise (n=266): 16.5, 16.2, 18.4 CBT alone (n=286): 15.0, 12.9, 18.5 Exercise alone (n=265): 12.8, 13.6, 11.7 TAU (n=270): 9.3. 12.2, 11.5 OR (95%CI) for 7+ points PCS improvement vs TAU, adjusted for study design, pending disability claims, and baseline V/SF-36 physical component summary score: Exercise: 1.07 (0.63 to 1.82) CBT: 1.72 (0.91 to 3.23) Exercise + CBT: 1.84 (0.95 to 3.55)	MPQ-S: Of the 4 subscales: sensory, affective, pain right now, typical level of pain, affective pain was significantly reduced (P < 0.025) vs TAU in CBT arms: CBT alone: -0.43 CBT + Exercise: -0.50 All other findings not significant.	MFI: Both exercise arms (exercise, CBT+Exercise) significantly improved fatigue (P < 0.05) vs TAU on all 5 domains (general, physical, reduced activity, reduced motivation, mental fatigue). CBT alone: No significant changes from baseline on any of the 5 MFI domains.

Intervention and study characteristics[a]	Physical Health Overall	Pain	Fatigue
	Overall (marginal) effect, OR (95%CI) for 7+ points PCS improvement vs TAU: CBT (n=552) vs no CBT (n=535): 1.71 (95% CI, 1.15 to 2.53) Exercise (n=531) vs no exercise (n=556): 1.07 (95% CI, 0.76-1.50)		
Detox regimen[8] (n=22) vs waitlist (n=10) Total N=32 Tx duration: 4-6 weeks Observation: 3 months ROB: Some concerns	VF-36 PCS: Difference in score (95% CI) between Waitlist and Tx at Week 6, adjusted for baseline (Positive changes indicate improvement): 6.9 (-0.3 to 14.2); P=0.06 Subscales of VF-36 physical: Physical functioning : 2.7 (-18.1 to 23.5) P=0.8 Role-physical: 27.6 (6.9, to 48.3) P=0.009 General health: 20.7 (9.2 to 32.3) P < 0.001 Vitality: 31.2 (15.6 to 46.9) P < 0.001	MPQ-2-SF: Difference in score (95% CI) between Waitlist and Tx at Week 6, adjusted for baseline (Negative changes indicate improvement): Total pain score: -1.1 (-2.0 to -0.2); P=0.02. VR-36 bodily pain subscale score: 26.4 (8.5, 44.4) P=0.004	MFI: Difference in score (95% CI) between Waitlist and Tx at Week 6, adjusted for baseline (Negative changes indicate improvement): General fatigue: -4.3 (-7.4 to -1.3); P=0.006 Physical fatigue: -3.5 (-6.9 to -0.2); P=0.04 Reduced activity: -4.0 (-7.3 to -0.7); P=0.02 Reduced motivation: -3.1 (-5.6 to -0.5); P=0.02 Mental fatigue: -5.7 (-8.7 to -2.7); P < 0.001
Mindfulness-based stress reduction[9] (n=26) vs TAU (n=29) Total N=55 Tx duration: 8 weeks Observation: 6 months ROB: Some concerns	NR	MPQ-2: Tx group reported greater reductions in pain at 6 months compared to TAU: Post-treatment: f=0.13; P=.45 6 months: f=0.33; P=.05	MFI General Fatigue: Tx group reported significant improvement in fatigue at 6 months compared to TAU: Post-treatment: f=0.18; P=0.27 6 months: f=0.32; P=0.03 PROMIS fatigue: significant improvement with Tx vs TAU at both timepoints: Post-treatment: f=0.35; P=0.02 6 months: f=0.26; P=0.05
Sleep focused mind-body bridging[10] (n=33) vs sleep education (n=27) Subpopulation: sleep disturbance Total N=60 Tx duration: 3 sessions over 3 weeks Observation: 3 months ROB: Some concerns	PA-assessed physical condition (N (%) improved): 8 (32%) vs 3 (13.6%); P=NS	QoL (SF-36 pain): Pre: 38.9 (30.8–47.0) vs 37.9 (29.5–46.2) Post: 46.6 (37.9–55.4) vs 39.1 (30.0–48.3) Observation: 45.0 (36.6–53.5) vs 39.5 (28.6–50.4)	Post-randomization treatment by period interaction: effect size 0.47 (P=0.032). The 2 interventions differed at Observation (p=.052), in which improvement in mental fatigue for MBB (1.99) was greater than that for SED (.36), from the baseline covariate (17.74). MFI, unadjusted mean (95% CI):

Intervention and study characteristics[a]	Physical Health Overall	Pain	Fatigue
			General fatigue: Pre: 21.0 (20.1 to 21.9) vs 20.7 (19.3 to 22.0) Post: 19.4 (18.1 to 20.8) vs 20.0 (18.7 to 21.3) Observation: 18.8 (17.3–20.4) vs 20.2 (18.4–22.0) Mental fatigue: Pre: 18.3 (17.2 to 19.5) vs 17.4 (15.9 to 18.9) Post: 16.2 (14.7 to 17.7) vs 16.2 (14.5 to 17.9) Observation: 16.1 (14.5 to 17.7) vs 17.1 (15.4 to 18.8)
Other interventions			
Acupuncture[11] 2x/week (n=52) vs 2-month waitlist then acupuncture 1x/week (n=52) Total N=104 Tx duration: 6 months Observation: 6 months ROB: Some concerns	SF-36P significantly improved by mean 9.4 points with T vs waitlisted group at month 6, adjusted for baseline pain. (P=0.03).	MPQ: at 6 months, treatment group had an average reduction of 3.6 points (p=0.04) compared to the comparator group.	NR
CPAP[12] (n=9) vs sham CPAP (n=9) Subpopulation: sleep-disordered breathing Total N=18 Tx duration: 3 weeks Observation: 3 weeks ROB: Low	Treatment group experienced 34% improvement in physical health. SF-36 PCS: between groups effect size 2.79 (P=0.0003) Correlation with sleep stage shifts: -0.41 (P=0.104)	Treatment group experienced 34% reduction in pain. Pain VAS (0-10, daily): between groups effect size 2.14 (P=0.0008) Correlation with sleep stage shifts: 0.51 (P=0.037)	Treatment group experienced 38% reduction in fatigue. FSS (increasing impact was rated 1–7 days 1 and 7 (averaged)): between groups effect size 2.55 (P=0.0002) Correlation with sleep stage shifts: 0.71 (P=0.0002)

[a]Study characteristics include number randomized per treatment arm, subpopulation if applicable, total sample size, duration of treatment, duration of observation (includes treatment period unless otherwise specified), and risk of bias (ROB).

Abbreviations: CBT=Cognitive Behavioral Therapy; CFS=Chronic Fatigue Syndrome; CGIS=Clinical Global Impressions Scale; CI=Confidence Interval; CPAP=Continuous Positive Airway Pressure; f=Cohen's f value (0 .10=small; 0.25=medium; 0.40=large effect size); FSS=Fatigue Severity Scale; GSRH=General Self-Reported Health; IBS=Irritable Bowel Syndrome; MBB=Mind-Body Bridging; MFI=Multidimensional Fatigue Inventory; MPQ=McGill Pain Questionnaire; NR=Not Reported; NS=Not Significant; P=P-value; PA=Physician's Assistant; PCS=Physical Component Summary; PROMIS=Patient-Reported Outcomes Measures Information System; ROB=Risk of Bias; QoL=Quality of Life; ROB=Risk of Bias; SED=Sleep Education; SF-36=36-item Short Form Survey (SF-36P=physical component); TAU=Treatment as Usual; Tx=Treatment; VAS=Visual Analog Scale; VSF-36 (also VF-36)=Veterans 36-Item Short Form Survey

Table 10. Results for cognitive, mental health, PTSD symptoms, and global outcomes in intervention trials for Gulf War Illness

Intervention and study characteristics	Cognitive symptoms	Mental health overall	Depression	Global outcomes (Function, QoL)	PTSD symptoms
Medications					
Doxycycline[1] (n=245) vs placebo (n=246) Subpopulation: positive mycoplasma DNA test N=491 Tx duration: 12 months Observation: 18 months ROB: Low	CFQ: N analyzed: 207 vs 214 Least-square mean difference at 12 months, Tx minus C (95% CI): -1.2 (-3.7 to 1.4), P > 0.2	Veterans SF-36 MCS: N analyzed: 199 vs 212 Least-square mean difference at 12 months, Tx minus C (95% CI): 0.0 (-1.8 to 1.8), P > 0.2	NR	NR	NR
Mifepristone[2] (n=18 in each phase 1 and 2) vs placebo (n=18 in phase 1, n=15 in phase 2), 6-week crossover Tx phases separated by 1-month washout Phase 1 N=36 Phase 2 N=33 Tx duration: 6 weeks Observation: 4 months ROB: Some concerns	MATRICS Consensus Cognitive Battery (Overall mean change, ΔT minus ΔC (SD)): 0.10 (6.83), P=0.937 Working memory: 0.16 (8.26), P=0.914 Verbal learning: 5.23 (10.29), P=0.008 Visual learning: -0.94 (11.12), P=0.643 Overall: 0.10 (6.83), P=0.937 CFQ Overall mean change, ΔT minus ΔC (SD): 1.06 (15.46), P=0.700	SF-36 MCS overall mean change, ΔT minus ΔC (SD): -1.89 (12.49), P=0.423	BDI overall mean change, ΔT minus ΔC (SD): 0.88 (9.22), P=0.595	NR	PCL overall mean change, ΔT minus ΔC (SD): -3.38 (12.26), P=0.130
Naltrexone[3] vs placebo (n's=NR), crossover phases separated by 1-month washout. Total N=40 Tx duration: 3 months Observation: 7 months ROB: High	Attention-related problems (CPT; mean change in hit response time): −7.33 ± 6.92 (95% CI: −21.49 to 6.72) vs −0.88 ± 7.98 (95% CI: −15.3 to 17.09) (P=0.43)	NR	NR	NR	NR
Rifaximin[4] (n=27) vs placebo (n=23) Subpopulation: IBS (Rome III)	NR	NR	NR	IBS-QoL, change mean (SE), Tx vs C: Dysphoria: 6.62 (4.31) vs 11.30 (4.82), P=0.50 Interference with activity: 8.40 (5.10) vs	NR

Intervention and study characteristics	Cognitive symptoms	Mental health overall	Depression	Global outcomes (Function, QoL)	PTSD symptoms
N=50 Tx duration: 2 weeks Observation: 2 weeks ROB: Some concerns				4.95 (4.76), P=0.52 Body image: 8.09 (4.14) vs 12.02 (4.93), P=0.83 Health worry: 3.92 (4.29) vs 10.26 (5.35), P=0.39 Food avoidance: 7.35 (6.35) vs 6.41 (5.27), P=0.26 Social reaction: 4.78 (4.14) vs 0.48, P=0.28 Sexual score: 3.68 (6.59) vs −3.85 (4.98), P=0.77 Relationships: 2.19 (3.54) vs −3.65, P=0.17 Overall (all items): 6.23 (4.00) vs 6.50 (3.82), P=0.86	
Nutritional Supplements					
Carnosine[5] (n=12 finished study) vs placebo (n=13 finished study) N=34 Tx duration: 12 weeks Observation: 14 weeks ROB: High	Cognition (WAIS-R digit symbol substitution test): Significant improvement within carnosine group between week 0 - 12 (P=0.046) vs no change with placebo. Trail Making Tests: No difference between groups	NR	NR	NR	NR
CoQ10[6] Q100 (n=11) vs Q300 (n=12) vs placebo (n=23) N=46 Tx duration: 3.5 +/- 0.5 months Observation: 3.5 +/- 0.5 months ROB: High	Backward digit span, change from baseline, mean diff (SE): Q100 (n=11) vs placebo (n=20): -0.13 (0.71); 95% CI -1.57 to 1.32, P=0.86 Q300 (n=11) vs placebo (n=20): -0.22 (0.85); 95% CI -1.96 to 1.53, P=0.80	NR	NR	NR	NR

Intervention and study characteristics	Cognitive symptoms	Mental health overall	Depression	Global outcomes (Function, QoL)	PTSD symptoms
Psychological, exercise, or multi-component interventions					
CBT+Exercise[7] (n=266) vs CBT (n=286) vs Exercise (n=265) vs TAU (n=270) Total N=1092 Tx duration: 12 weeks Observation: 12 months ROB: Some concerns	CFQ (positive changes indicate improvement) Mean changes from baseline, adjusted for study design, pending disability claims, and baseline values: TAU: -0.67 (P=NS) CBT + Exercise: 3.38 (P < 0.01) Exercise: 2.98 (P < 0.01) CBT: 2.66 (P < 0.025)	VSF-36 MCS score: Mean change from baseline, adjusted for study design, pending disability claims, and baseline values ((positive changes indicate improvement): TAU: -1.03 (P=NS) CBT + Exercise: 2.30 (P < 0.01) Exercise: 2.33 (P < 0.01) CBT: 0.97 (P < 0.025) VSF-36 Mental Health Index: TAU: -1.60 (P=NS) CBT + Exercise: 2.95 (P < 0.01) Exercise: 3.27 (P < 0.01) CBT: 1.37 (P=NS)	NR	NR	NR
Detox regimen[8] (n=22) vs waitlist (n=10) N=32 Tx duration: 4-6 weeks Observation: 3 months ROB: Some concerns	NR	VF-36 MCS (Positive changes indicate improvement): Difference in score (95% CI) between Waitlist and Tx at Week 6, adjusted for baseline: 9.5 (3.1 to 15.8); P=0.003 Role-emotional: 15.2 (-4.9 to 35.2) P=0.1 Mental health: 17.7 (5.3 to 30.0) P=0.005	NR	Subscales of VF-36 mental: Social functioning: 15.9 (-3.9 to 35.7) P=0.1	NR
Mindfulness-based stress reduction[9] (n=26) vs TAU (n=29) N=55 Tx duration: 8 weeks Observation: 6 months	CFQ: intervention group reported more cognitive failures post-treatment: f=0.44; P=.002 6 months: f=0.40; P < .001	NR	PHQ-9: reduction in depressive symptoms greater for treatment group, at both post-treatment and 6 months:	NR	PSS-I: reduction in PTSD symptoms greater for treatment group post-treatment, but not 6 months: Post-treatment:

Intervention and study characteristics	Cognitive symptoms	Mental health overall	Depression	Global outcomes (Function, QoL)	PTSD symptoms
ROB: Some concerns			Post-treatment: f=0.22; P=.050 6 months: f=0.27; P=.031		f=0.40; P=0.004 6 months: f=0.27; P=0.08 Veterans with PTSD at baseline (N=45) randomized to treatment group had significantly greater reductions in PTSD symptoms vs TAU post-treatment, but not 6 months: Post: f=0.44; P=.005 6 months: f=0.31; P=.082
Sleep focused mind-body bridging[10] (n=33) vs sleep education (n=27) Subpopulation: sleep disturbance N=60 Tx duration: 3 sessions over 3 weeks Observation: 3 months ROB: Some concerns	Cognitive failure (CFQ total score), unadjusted means (95% CI): Pre: (51.7 to 62.5) vs 55.9 (46.2 to 65.6) Post: 49.9 (42.4 to 57.3) vs 46.0 (35.1 to 57.0) At 3 months: 50.6 (40.6 to 60.6) vs 46.7 (35.6 to 57.9) "no reliable treatment effects"	BSI (global severity index), unadjusted means (95% CI): Pre: 24.8 (20.5 to 29.0) vs 25.4 (20.3 to 30.4) Post: 23.0 (18.2 to 27.9) vs 20.4 (14.1 to 26.6) At 3 months: 20.2 (15.6 to 24.9) vs 23.5 (16.1 to 30.9) "no reliable treatment effects"	Depression (CES-D total score), unadjusted means (95% CI): Pre: 27.4 (25.2 to 29.5) vs 26.2 (23.2 to 29.2) Post: 25.4 (22.5 to 28.3) vs 24.9 (21.5 to 28.2) Observation: 22.8 (20.5 to 25.2) vs 27.0 (22.6 to 31.4) No between-groups difference for post randomization treatment (p=.17) or treatment by period interaction (p=.080). Observation: significantly greater improvement with MBB in customized	No treatment effects QoL (SF-36 total score), unadjusted means (95% CI): Pre: 43.8 (38.6 to 48.9) vs 43.0 (35.8 to 50.1) Post: 48.4 (42.6 to 54.1) vs 46.4 (39.6 to 53.2) Observation: 48.2 (42.0 to 54.4) vs 44.2 (35.82 to 52.5) QoL (SF-36 pain), unadjusted means (95% CI): Pre: 38.9 (30.8 to 47.0) vs 37.9 (29.5 to 46.2) Post: 46.6 (37.9 to 55.4) vs 39.1 (30.0 to 48.3) Observation: 45.0 (36.6.0 to 53.5) vs 39.5 (28.6 to 50.4)	PCL-M total score adjusted mean improvement: MBB Post-Tx: 3.30 (p=.027) 3m observation: 5.45 (p=.001) SED Post-Tx: not significant (P=0.72) 3m observation: not significant (P=0.19). The 2 groups differed for the post randomization treatment effect (p=.038). MBB was more effective than SED in decreasing PCL-M scores.

Intervention and study characteristics	Cognitive symptoms	Mental health overall	Depression	Global outcomes (Function, QoL)	PTSD symptoms
			between-groups contrasts (adjusted mean): effect size=0.71 (P=.038)		
Other interventions					
CPAP active[12] (n=9) vs sham CPAP (n=9) Subpopulation: sleep-disordered breathing N=18 Tx duration: 3 weeks Observation: 3 weeks ROB: Low	Treatment group experienced 33% improvement in cognitive function. Cognitive VAS (0-10 daily): between groups effect size 1.67 (P=0.004) Cognition correlation with sleep stage shifts: 0.64 (P=0.006)	Treatment group experienced 16% improvement in mental health. SF-36 mental: between groups effect size 1.29 (P=0.03) Correlation with sleep stage shifts: -0.58 (P=0.015)	NR	NR	NR

[a]Study characteristics include number randomized per treatment arm, subpopulation if applicable, total sample size, duration of treatment, duration of observation (includes treatment period unless otherwise specified), and risk of bias (ROB).

Abbreviations: BDI=Beck Depression Inventory; BSI=Brief Symptom Inventory; CBT=Cognitive Behavioral Therapy; CES-D=Center for Epidemiological Studies-Depression Scale; CFQ=Cognitive Failures Questionnaire; CI=Confidence Interval; CPAP=Continuous Positive Airway Pressure; CPT=Connors Continuous Performance Test; f=Cohen's f value (0 .10=small; 0.25=medium; 0.40=large effect size); IBS-QoL=Irritable Bowel Syndrome Quality of Life; MATRICS=Measurement and Treatment Research to Improve Cognition in Schizophrenia; MBB=Mind-Body Bridging; MCS=Mental Component Score; NR=Not Reported; P=P-Value; PCL=PTSD Checklist; PHQ-9=Patient Health Questionnaire 9-item; PSS-I=PTSD Symptom Score interview; PTSD=Post-Traumatic Stress Disorder; QoL=Quality of Life; ROB=Risk of Bias; SE=Standard Error; SED=Sleep Education; SF-36=36-Item Short Form Survey; TAU=Treatment as Usual; Tx=Treatment; VAS=Visual Analog Scale; VSF-36 (also VF-36)=Veterans 36-Item Short Form; WAIS-R-Wechsler Adult Intelligence Scale-Revised

Table 11. Results for gastrointestinal symptoms and sleep outcomes in intervention trials for Gulf War Illness

Intervention and study characteristics[a]	Gastrointestinal Symptoms	Sleep Outcomes
Medications		
Rifaximin[4] (n=27) vs placebo (n=23) Subpopulation: IBS (Rome III) N=50 Tx duration: 2 weeks Observation: 2 weeks ROB: Some concerns	IBS symptoms (BDQ) - difference (T minus C, change from baseline), (95% CI), P value: Stool frequency: 0.2 (−0.2, 0.6), P=0.38 Stool consistency: 0.3 (− 0.2, 0.9), P=0.25 Urgency: 0.0 (−0.2, 0.3), P=0.88 Abdominal pain: 0.1 (− 0.4, 0.7), P=0.71 Bloating: 0.1 (−0.5, 0.6), P=0.86 Global improvement: 0.0 (−0.6, 0.6), p > 0.99	NR
Nutritional Supplements		
Carnosine[5] (n=12 finished study) vs placebo (n=15 finished study) N=27 Subpopulation: IBS (Rome II) Tx duration: 12 weeks Observation: 14 weeks ROB: High	Within groups: Tx group had reduced stool frequency and watery consistency from weeks 0 to 12 (P=0.019) vs no changes in placebo group.	NR
Psychological, exercise, or multi-component interventions		
Sleep focused mind-body bridging[10] (n=33) vs sleep education (n=27) Subpopulation: sleep disturbance N=60 Tx duration: 3 sessions over 3 weeks Observation: 3 months ROB: Some concerns	NR	Adjusted mean SPI-II scores were similar between SED and MBB for the overall treatment effect (p=.32). Sleep problems in MBB declined to a greater extent than did those in SED (p=.046, effect size=.70). The adjusted mean improvements, MBB vs SED: Post-treatment: 16.88 vs 14.69 At 3 months: 20.70 vs 12.63 All were sig. different from baselines (p < .001). PA-assessed changes in sleep, SED vs MBB (P for between group difference): Improved: 7 (26.9%) vs 17 (58.6%), P <0.05
Other interventions		
CPAP active[12] (n=9) vs sham CPAP (n=9) Subpopulation: sleep-disordered breathing	NR	Quality of sleep (PSQI; rated 0–21 on days 1 and 7 (averaged)): Treatment group experienced 41% improvement. Slightly poorer in sham group (assessed by sleep parameters), but no significant between-group differences.

Intervention and study characteristics[a]	Gastrointestinal Symptoms	Sleep Outcomes
N=18 Tx duration: 3 weeks Observation: 3 weeks ROB: Low		PSQI: between groups effect size 2.67 (P=0.0003) Correlation with sleep stage shifts: 0.59 (P=0.016)

[a]Study characteristics include number randomized per treatment arm, subpopulation if applicable, total sample size, duration of treatment, duration of observation (includes treatment period unless otherwise specified), and risk of bias (ROB).

Abbreviations: BDQ=Bowel Disease Questionnaire; CBT=Cognitive Behavioral Therapy; CI=Confidence Interval; CPAP=Continuous Positive Airway Pressure; IBS=Irritable Bowel Syndrome; MBB=Mind-Body Bridging; NR=Not Reported; P=P-value; PSQI=Pittsburgh Sleep Quality Index; ROB=Risk of Bias; SED=Sleep Education; SPI-II=Stroke Prognosis Instrument 2.

Table 12. Adverse events in published intervention studies for Gulf War Illness

Treatment (Sample size)	N participants	Adverse events
Acupuncture[11]	104	1 in biweekly treatment group reported pain on needling; 1 in weekly treatment group reported suicidal thoughts
Carnosine[5]	34	1 asymptomatic elevation of alanine-serine transaminase plus interval increase in CRP, considered not related to study drug.
CBT, Exercise, CBT + Exercise[7]	1092	112 serious AEs, mostly "hospitalizations unrelated to the study": 23 CBT + exercise 27 exercise 30 CBT 32 TAU 3 AEs possibly related: 2 TAU (psychosis and angina) 1 back surgery (exercise arm)
CoQ10[6]	46	2 neurological events, both placebo.
CPAP[12]	18	---
Detox regimen[8]	32	Discomfort and nausea from sauna; flushing and itching from niacin; pre-syncope; IBS; hypokalemia
Doxycycline[1]	491	Significantly more nausea and photosensitivity with doxycycline vs placebo. No significant difference in myalgia.
Mifepristone[2]	36	1 on mifepristone developed a rash that resolved after ceasing drug
Mindfulness-based stress reduction[9]	55	---
Naltrexone[3]	40	1 w/d due to dizziness with naltrexone.
Rifaximin[4]	50	No differences
Sleep focused mind-body bridging vs sleep education[10]	60	---

Abbreviations: CBT=cognitive behavioral therapy; CPAP=continuous positive airway pressure; CoQ10= coenzyme Q10; TAU=treatment as usual.

Table 13. Details of ongoing and unpublished controlled trials of interventions/management strategies for Gulf War Illness

Intervention; Registration; Study Design; Sponsors; Setting	Study Title	Status; completion date	Purpose of study	Participants; Intervention(s)/ Comparator	GWI case definition	Outcome(s) and timing
Behavioral						
CBT[26] NCT02782780 RCT VA ORD; San Francisco VAMC	Cognitive Behavioral Therapy for Insomnia for Gulf War Illness	Recruiting as of July 2019; E: May 30, 2020	"examine the efficacy of telephone-delivered CBTi for alleviating sleep and non-sleep GWI symptoms in a 2-arm randomized controlled trial"	80 deployed GW Veterans meeting Gulf War Registry criteria, Kansas definition, and Insomnia severity index score of 14 or greater 8 weekly, individual sessions of Cognitive Behavioral Therapy for Insomnia (CBTi) vs usual care/waitlist	Kansas	1°: Insomnia severity (ISI); sleep quality (PSQI); GWI symptoms (modified Kansas questionnaire); sleep latency, minutes of wake after sleep onset, sleep efficiency (self-report sleep diary) 2°: fatigue (FSS); pain (BPI); cognitive function (MASQ); anxiety and depressive symptoms (HADS) Time frame: baseline, 8 weeks, and 6-month follow-up
Cognitive rehabilitation[27] NCT02161133 RCT VA ORD; VAMCs Bedford, MA; East Orange, NJ; Canandaigua, NY	Cognitive Rehabilitation for Gulf War Illness	Completed Sept 2019. No results; A: September 1, 2019	"to determine whether Problem-Solving Therapy, a patient centered cognitive rehabilitation therapy, can reduce disability by compensating for problem-solving deficits"	268 GW Veterans with GWI, scores at least half a standard deviation worse than the mean on the WHODAS 2.0 Cognitive rehab (problem-solving therapy) vs Health education	Kansas	1°: Disability (WHODAS 2.0) 2°: problem-solving inventory (self-report), problem-solving ability (Neuropsychological Battery includes: Halstead Category Test, Russell Revised Version; CPT-3, Stroop Color and Word Test, executive functioning (TMT parts A and B), FIT, fatigue (FSS), and pain (PDI and MPI composite score) Time frame: 12 weeks
MBSR[28] NCT03058952 RCT VA ORD; VAPSHCS, Seattle, WA	Evaluation of a Mindfulness-Based Intervention for Gulf War Illness	Recruiting as of July 2017; E: April 30, 2021	"to evaluate outcomes of… Mindfulness-Based Stress Reduction and an adapted version of the Chronic Disease Self-Management Program (CDSMP)…for Veterans with Chronic Multisymptom Illness (CMI)."	308 Veterans with CMI (50% will be GWV*) MBSR vs adapted CDSMP	N/A (used CMI as criteria)	1°: Pain (SF-MPQ-2); Fatigue (MFI); concentration and memory (CFQ); satisfaction with intervention (CSQ-8) 2°: Depression (PHQ-9); PTSD (PCL-C); SF-36; alcohol use disorder (NIH PROMIS Alcohol Use and Negative Consequences, short form)

Intervention; Registration; Study Design; Sponsors; Setting	Study Title	Status; completion date	Purpose of study	Participants; Intervention(s)/ Comparator	GWI case definition	Outcome(s) and timing
Central Nervous System (CNS) Stimulation						
rTMS[23] NCT01608321 RCT VA ORD; VA Palo Alto Health Care System	rTMS for the Treatment of Chronic Pain in GW1 Veterans (rTMS)	Terminated (Did not meet recruitment goals as of June 2015)	"to engage in a clinical trial of rTMS in chronic pain that occurs in the context of multiple medical symptoms …in GWI diagnosed patients [with] symptoms of chronic pain in the musculoskeletal category and at least two additional symptoms."	206 (initially estimated) Chronic pain >= 4 on the pain severity scale of the BPI-SF Active vs sham rTMS, 20 sessions	Kansas	1°: Change in pain (BPI-SF) Time Frame: Baseline and 3-4 weeks
rTMS[31] NCT03030794 RCT Veterans Medical Research Foundation, in collaboration with DoD; Naval Medical Center and Veterans Affairs Hospital, San Diego, CA	Alleviating Headache and Pain in GWI With Neuronavigation Guided rTMS	recruiting as of Aug 2018; E: December 2018	"assess the effect of repetitive transcranial magnetic stimulation (rTMS) on Gulf War illness related headaches and pain"	90 pts meeting CDC and Kansas criteria with Migraines and muscle pain and joint pain Repetitive transcranial magnetic stimulation (rTMS), 11 visits over 2 months vs Sham rTMS at same intervals	CDC and Kansas	1°: Self-reported headache and pain (daily log); HA pain severity (HIT-6); pain level; opioid medication assessment; headache, muscle, and joint pain (VAS) 2°: Neurobehavioral symptoms (NSI); Pain (SF-MPQ); widespread pain (New Clinical Fibromyalgia Diagnostic Criteria); FIQR; HVLT; TMT A&B; executive function; depression (HAM-D); SF-36; sleep quality (PSQI); insomnia fatigue scale Time Frame: 2 months for each subject (11 visits)
rTMS[32] NCT04046536 RCT VA ORD; VA San Diego, Palo Alto, and Atlanta	rTMS in Alleviating Pain and Co-Morbid Symptoms in Gulf War Veterans Illness (GWVI)	Recruiting as of Nov 2019 E: September 30, 2024	Assess "effectiveness of using repetitive transcranial magnetic stimulation (rTMS) in relieving pain and other co-morbid symptoms of Gulf War Illness"	80 GW Veterans meeting CDC and Kansas, with migraines, muscle and joint pain, and depression 4 arms: 1. rTMS at the LDLPFC 2. rTMS at the LMC vs	CDC and Kansas	1°: Self-reported headache and pain by daily log; SF-MPQ; HIT-6; HAM-D; SF-36; BPI-SF; pain (New Clinical Fibromyalgia Diagnostic Criteria); FIQR; sleep quality (PSQI); insomnia severity index; Flinders Fatigue Scale 2°: PTSD symptoms (CAPS-5); opioid-based pain medication usage; supraspinal resting state

Intervention; Registration; Study Design; Sponsors; Setting	Study Title	Status; completion date	Purpose of study	Participants; Intervention(s)/ Comparator	GWI case definition	Outcome(s) and timing
				3. Sham rTMS at the LDLPFC 4. Sham rTMS at the LMC		functional connectivity (MRI) Time Frame: Baseline, 1-week, 1-month, 2-month, and 3-month
rTMS[33] NCT04182659 RCT Veterans Medical Research Foundation & DoD; VA Palo Alto, San Diego, Atlanta	Long Term Efficacy of Neuronavigation Guided rTMS in Alleviating Gulf War Illness Related Headaches and Pain Symptoms	Recruiting as of Dec 2019; E: Sept 2022	Assess "the effectiveness of repetitive transcranial magnetic stimulation (rTMS), non-invasive treatment option, in alleviating headaches, muscle, and joint pain symptoms of GWI."	150 GW Veterans with migraines, under age 65, who served at least 30 days in the conflict Transcranial Magnetic Stimulation (rTMS) vs sham rTMS at the left motor cortex (LMC)	CDC & Kansas	1°: pain (SF-MPQ; BPI-SF), headaches (Self-report journal; HIT-6), QoL (SF-36); fibromyalgia (New Clinical Fibromyalgia Diagnostic Criteria - Part 1; Revised Fibromyalgia Impact Questionnaire); neurobehavioral (NSI); sleep (PSQI; Insomnia Severity Index); fatigue (Flinders Fatigue Scale). 2°: PTSD (CAPS-5); opioid-based pain medication usage; supraspinal resting state functional connectivity
(HD) tDCS[30] NCT03542383 RCT The University of Texas at Dallas; Callier Center for Communication Disorders	Treatment of Memory Disorders in Gulf War Illness with High Definition Transcranial Direct Cortical Stimulation	Recruiting as of May 2018; E: Sept 29, 2019	"determine if delivery of [High Definition transcranial Direct Current Stimulation] HD tDCS over the [PreSupplementary Motor Area] preSMA will improve performance in GWI veterans with a verbal retrieval deficit"	120 deployed GW Veterans HD tDCS: 10 20-minute sessions of 1 mA anodal High Definition Transcranial Direct Current Stimulation to the preSMA region over a 2-week period vs sham HD tDCS at same duration	Not specified	1°: Verbal fluency (COWAT; timing note: also applied at initial phone screen), and Verbal learning and memory (CVLT) 2°: Semantic memory (SORT); Semantic Selection Task Time Frame: Baseline, after Tx (2 weeks), and 3- and 6-months follow-up
tDCS[34] NCT03547869 RCT The University of Texas at Dallas; University of Texas Southwestern Medical Center	Transcranial Direct Current Stimulation for Pain Treatment in Gulf War Illness.	Recruiting as of July 2019; E: March 12, 2021	"investigate long-term modulation of pain pathways leading to a suppression of pain symptoms in Gulf War Illness patients by applying transcranial direct current stimulation"	120 GW Veterans tDCS vs sham tDCS, 10 sessions	Not specified	1°: Pain (VAS) 2°: Brain activity (EEG) Time frame: baseline, immediately after tDCS, and 1, 4, 12, 24 weeks after the last tDCS session
VNS[35] NCT02791893 RCT	Vagus Nerve Stimulation: Treatment for	Recruiting as of Nov 2019;	"Besides their pain, the researchers will also assess the effect of	40 GWV with GWI, widespread pain, has migraine headaches	Kansas	1°: Widespread pain (VAS); 2°: Overall improvement (patient global improvement of change),

Intervention; Registration; Study Design; Sponsors; Setting	Study Title	Status; completion date	Purpose of study	Participants; Intervention(s)/ Comparator	GWI case definition	Outcome(s) and timing
Benjamin Natelson VA East Orange, NJ; Icahn School of Medicine at Mount Sinai	Gulf Veterans with Gulf War Illness	E: March 2020	vagus nerve stimulation (VNS) in alleviating migraine headache"	VNS hand-held device (20 weeks total, 120 second period 3x/day) vs placebo (inactive device at same frequency/duration)		SF-36, number of migraine headache days Time frame: baseline, 10 and 20 weeks
Complementary and integrative health						
Acupressure[36] NCT02075489 NRCT The Cleveland Clinic	Acupressure for Pain Management and Fatigue Relief in Gulf War Veterans	Completed Oct 2017. No results; A: October 2017	"determine the effectiveness of acupressure treatment in symptomatic veterans in fatigue relief and pain management for Gulf War Illness (GWI)"	7 GW Veterans with GWI, severity and interference scores of 5+ by BPI, score of 3+ by Piper Fatigue Scale Acupressure treatment (40 minutes/day, 2days/week for 6 weeks) vs Reiki (40 mins/day, 2 days/week for 6 weeks)	Not specified	1°: Fatigue (revised PFS) 2°: changes in corticomuscular coherence (EEG and EMG surface signals), SF-36 Timing: baseline and 6 weeks
Meditation + acupuncture[37] NCT02180243 RCT VA ORD; VAMC, Washington, DC	CAM in Veterans with Gulf War Illnesses	Recruiting as of Nov 2019; E: October 1, 2021	"to explore the effectiveness Gulf War Health Education (GWHE) and iRest Yoga Nidra (meditation)/ auricular (ear) acupuncture for Veterans with Gulf War Veterans' Illnesses (GWVI)"	172 GW Veterans with GWI (*ie* fatigue, pain, cognitive impairment) iRest Yoga Nidra and auricular acupuncture vs Gulf War Health education	Not specified	1°: Sleep quality (objective and self-report sleep measures will be taken) Time frame: 1 year
Tai Chi[38] NCT02661997 RCT VA ORD; VAMC Boston	Novel Interventions for GWVI	Recruiting as of Aug 2, 2019; E: March 31, 2021	"examine the beneficial effects of two novel treatments for Gulf War Veteran's Illness (Tai Chi and Wellness intervention) and to establish the efficacy of these mind-body approaches to symptom reduction"	120 GW veterans with joint pain or stiffness over 6 months and meeting CDC CMI criteria Tai Chi: 60 minutes, twice a week for 12 weeks + 30min/day home practice vs Wellness Intervention: same dose/duration + VA Whole Health video and brief mindfulness practice	CDC	1°: Change in pain (BPI-SF) 2°: Fatigue (MFI-20); PROMIS Global Health Scale; 50-foot walk test; Short Physical Performance Battery; executive functioning (TMT); verbal learning (HVLT-R) Other outcomes: various Time frame: baseline and 12 weeks

Intervention; Registration; Study Design; Sponsors; Setting	Study Title	Status; completion date	Purpose of study	Participants; Intervention(s)/ Comparator	GWI case definition	Outcome(s) and timing
Yoga[39] NCT02378025 RCT Palo Alto Veterans Institute for Research, DoD VAMC, Palo Alto	Treating Chronic Pain in Gulf War Illness	Completed; A: March 2018 Results shown in Table 14	"The purpose of this study is to determine whether yoga is effective for the treatment of chronic pain in Gulf War Illness"	75 Veterans (served 1990-91 regardless of deployment) with chronic pain Yoga (10 weeks) vs CBT (10 weeks)	CDC	1°: Pain (BPI-SF) Time frame: Weeks 0, 2, 4, 8, 10, 18, 26, and 34 2°: SF-36, Fatigue (6-minute walk test), Changes in medication. Time frame: Weeks 0, 10, and 34
Diet						
Low-FODMAP diet[25,40] NCT02881944 RCT Ashok Tuteja VAMC Salt Lake City, UT	Effect of Diet on Gulf War Illness	Completed E: September 2018 Results shown in Table 14	"compare a low FODMAP diet to a high FODMAP diet for effect on Veterans with IBS and symptoms of Gulf War Illness"	68 GW Veterans with IBS and 2 or more of the non-intestinal symptom groups (chronic-once a week or more often-fatigue, insomnia, joint pains, general stiffness, and headache, neurological and mood, respirator and skin symptoms) for > 6 months Low-FODMAP diet vs high-FODMAP (typical healthy) diet for 3 weeks	Not specified	1°: Bowel symptom score (self-reported) 2°: IBS-QoL score (self-reported) Time frame: baseline and 3 weeks
Low-glutamate diet[41,42] NCT03342482 Crossover RCT American University, Washington, DC	Glutamate Neuro-Excitotoxicity in GWI	Recruiting as of July 4, 2019; E: August 31, 2020	"test the effectiveness of a low-glutamate diet in GWI patients, as a way to mediate symptom occurrence by reducing excess glutamatergic neurotransmission"	40 Veterans deployed during GW with GWI Phase 1: Low-glutamate diet vs waitlist (1 month) Phase 2: MSG challenge (3 consecutive days) vs placebo (2 weeks: one 3-day challenge per week, then crossover)	Kansas and CDC	1°: Change in Brain Glutamate Levels (MRS) at baseline and 1 month 2°: Symptom change, and Cognitive function (computerized battery) Other: Change in brain excitation (EEG) Timing (2° and other): baseline, 1 month, and weeks 5 & 6
Exercise						
Exercise training[43] NCT01350492 RCT	Impact of Exercise Training on Pain and Brain Function in	Completed. No results posted as of April 5, 2019;	"test the influence of weight training on physical symptoms, physical activity and brain structure and function in	77 Gulf War Veterans with chronic musculoskeletal pain Resistance exercise training (16 weeks) vs	Not specified	1°: Symptoms (self-report and EHR) 2°: Physical activity (accelerometer and self-report),

Intervention; Registration; Study Design; Sponsors; Setting	Study Title	Status; completion date	Purpose of study	Participants; Intervention(s)/ Comparator	GWI case definition	Outcome(s) and timing
VA ORD; VAMC Madison, WI	Gulf War Veterans	A: December 31, 2018	Gulf War Veterans with chronic widespread muscle pain"	Waitlist		brain structure and function (6 MRI scans over course of study) Time frame: baseline, during exercise phase, and 6- and 12-months post-exercise
Medications						
D-cycloserine[44] NCT02983734 RCT Boston University Charles River Campus	D-cycloserine: A Novel Treatment for Gulf War Illness (GWDCS)	Recruiting Jan 2019; September 2019	"investigate the efficacy of d-cycloserine (DCS) treatment for Gulf War Illness (GWI)"	56 GW Veterans meets GWI criteria with cognitive symptom domain D-cycloserine 100mg/day for 4 weeks vs placebo	Not specified	1°: Neuropsychological Test Battery 2°: Symptom Questionnaires Time frame: 8 weeks per subject
Etanercept+ mifepristone[45] NCT04254627 Phase I Nova Southeastern University, RTI International, Rochester General Hospital	Tumor Necrosis Factor (TNF) and Glucocorticoid Antagonist for Gulf War Illness (GWI)-Associated Multi-symptom Disease Homeostasis Reset	Not yet recruiting as of Mar 2020; E: July 2021	"assess the safety and mechanistic efficacy of a sequential etanercept-mifepristone intervention for Gulf War Illness"	20 males, 45-70 yrs, with trauma, meeting CDC & Kansas criteria for GWI Etanercept 50 mg weekly injection for 12 weeks, followed by 1 week of mifepristone at either 300 or 600 mg/day	CDC & Kansas	1°: Safety
Duloxetine vs pregabalin[24] NCT01846182 RCT VA ORD; Central Texas Health Care System and Central Texas VAMC (Waco, TX)	RCT of Duloxetine & Pregabalin for the treatment of Gulf War Illness in Veterans	Terminated Jan 2020	"Test the efficacy of Duloxetine and Pregabalin for treating Gulf War Veterans who suffer from GWI"	162 English-speaking GW Veterans with pain and GWI 3 arms: 60mg duloxetine (taken daily in AM) vs 300mg pregabalin (taken daily in PM) vs placebo (taken daily AM & PM), for 20 weeks	Kansas	1° Pain (10-point VAS; PCS of SF-36) 2°: Side effects (checklist) Time frame: every 2 weeks up to 34 weeks
Intranasal insulin[46] NCT01802944 RCT Bronx Veterans Medical Research	Intranasal Insulin: A Novel Treatment for Gulf War Multisymptom Illness	Unknown as of Oct 2017; E: December 2017	Examine whether intranasal insulin improves cognitive function and other CMI symptoms in GW Veterans with CMI	114 GW veterans with CMI, must include cognitive domain (Kansas)	Kansas	1°: Memory functioning (CVLT), and attention functioning (Stroop Color-Word Interference Task). Secondary: Physical health (PCS of the SF-12V), mood (POMS vigor scale)

Intervention; Registration; Study Design; Sponsors; Setting	Study Title	Status; completion date	Purpose of study	Participants; Intervention(s)/ Comparator	GWI case definition	Outcome(s) and timing
Foundation, Inc.; Bronx and Boston VAMCs				2 dose groups: 10 IU BID and 20 IU BID intranasal insulin vs placebo		Time frame: baseline, 8 weeks, and 1-month follow-up
Prednisone[47] NCT02506192 RCT Minneapolis VAMC; DoD is a collaborator	Gulf War Illness Inflammation Reduction Trial	Recruiting as of Aug 2019; E: October 2020	"determine if treatment with an anti-inflammatory drug (delayed-release prednisone) improves the health-related quality of life (HRQoL) of veterans with Gulf War Illness (GWI)"	100 GW vets deployed to Kuwaiti Theater of Operation, and scores moderate-severe on at least 3 out of 6 domains from the Kansas GWI case definition Delayed-Release Prednisone oral tablets (2x5mg) daily for 8 weeks vs placebo	Kansas	1°: SF-36 PCS. Time frame: 0, 8, and 16 weeks 2°: Pain (MPQ); Fatigue (MFI); Cognitive symptoms (CFQ); SF-36 MCS; blood biomarkers (MAP and CBC)
Pregnenolone[48] NCT01956279 RCT VA ORD; VA Durham, NC	Complementary Neurosteroid Intervention in Gulf War Illnesses (GWVI)	Completed Oct 2018; A: October 10, 2018	"investigate the use of adjunctive pregnenolone for" fatigue, musculoskeletal pain, and cognitive decline	170 GW deployed Veterans Pregnenolone: 250 mg BID for 28 days after titration phase (titration starting at 50mg BID increasing by 100mg every 2 wks) vs placebo	modified CDC	1°: SF-36 Physical component 2°: Pain (BPI); executive functioning (Tower of London from BAC-A); Fatigue (MFSI); psychiatric symptoms (SCL-90R) Time frame: baseline (2 weeks), 6 and10 weeks
Rituximab[49] GW160123 RCT DoD; Nova Southeastern University	The Use of B-Cell Depletion Therapy (BCDT) in Gulf War Illness: A Phase 1/2 Study	NR; NR	"to evaluate the efficacy and safety of rituximab, validate the presence of central nervous system autoantibodies and decrease their presence with B-cell depleting therapy such as rituximab, and reset underlying mechanisms of disease to improve symptoms and reset homeostasis.	NR Rituximab (2 infusions with 2 weeks' interval (500 mg/m2, max. 1000 mg)) vs Placebo: Saline infusion	Not specified	1°: SF-36 (PCS and vitality), and levels of autoantibodies against neuronal glial proteins Time frame: 6 weeks, and 3, 6, and 9 months after initial administration of rituximab or placebo
Nutritional supplements						

Intervention; Registration; Study Design; Sponsors; Setting	Study Title	Status; completion date	Purpose of study	Participants; Intervention(s)/ Comparator	GWI case definition	Outcome(s) and timing
Botanical Microglia Modulators[51] NCT02909686 Crossover RCT University of Alabama at Birmingham; CDMRP is a collaborator	Effects of Botanical Microglia Modulators in Gulf War Illness	Active as of Oct 2019; E: Sept 2020	test if any botanical agents that "suppress microglia function in a way that is anti-inflammatory and neuroprotective…suppress symptoms in GWI"	64 male GW Veterans with GWI Botanical compounds daily values: Boswellia serrata 400-800mg, curcumin 1000-2000mg, Epimedium 1000-2000mg, fisetin 200-800mg, luteolin 200-400mg, nettle 435-1305mg, Pycnogenol 200-400mg, reishi mushroom 1600-3200mg, resveratrol 200-600mg vs placebo	Kansas	1°: GWI severity (self-report scale: 0-100 2x/day) 2°: self-reported pain, fatigue, cognitive symptoms, mood, dermatological symptoms, respiratory symptoms, and GI symptoms Time frame: the last 2 weeks of each treatment, compared to average severity during the last 2 weeks of placebo; baseline
Concord grape juice[52] NCT02915237 RCT Icahn School of Medicine at Mount Sinai in collaboration with DoD; VA East Orange, NJ	Development of a Polyphenol-rich Dietary Preparation for Treating Veterans with Gulf War Illness	Completed Mar 2019. No results posted; A: January 17, 2019	"the goal is to test whether daily consumption of commercially available Concord grape juice is effective for treating cognitive deficits and chronic fatigue in Veterans with GWI"	36 GW Veterans with GWI Concord grape juice (low 4oz dose, moderate 8oz dose, and high 16oz dose) vs placebo beverage	Kansas	1°: Safety and tolerability to treatment (BSI and PHQ-15), cognitive functioning (CVLT-II), chronic fatigue (CFQ11) 2°: Auditory attention (WAIS-IV - digit span subtest), attention (CPT-3), graphomotor speed and executive functioning (TMT), intelligence level (WAIS-IV block design subtest), color and word test (Stroop test), Halstead Category Test, learning and memory (BVMT-R), auditory memory and attention (WAIS-IV) Time frame: 6 months
Mitochondrial cocktail[53] NCT02804828/ GW140146 Controlled trial (not clear if randomized) University of California, San Diego	Mitochondrial Cocktail for Gulf War Illness	Not yet recruiting as of Dec 2018; E: Sept 2019	"assess the benefit of a mitochondrial cocktail plus individualized correction of citric acid cycle (CAC) intermediates and amino acid (AA) abnormalities as part of a mitochondrial/ oxidative stress treatment	Meet CDC and Kansas GWI criteria Individualized mitochondrial cocktail & Arctic cod liver oil capsules vs placebo	CDC and Kansas	1°: Predictive GWI biomarkers (α-ketoglutarate, fumarate, malate, citrate, and isocitrate) Time Frame: baseline, 6, and 12 months

Intervention; Registration; Study Design; Sponsors; Setting	Study Title	Status; completion date	Purpose of study	Participants; Intervention(s)/ Comparator	GWI case definition	Outcome(s) and timing
			approach in Gulf War Illness (GWI)."			
Resveratrol[54] NCT03665740 RCT VISN 17 CoE, Waco, Texas	Multimodal Investigation of the Neuroprotective Effects of Resveratrol (MINER)	Recruiting as of Sept 2018; E: August 31, 2022	Examine whether "resveratrol treatment will improve memory issues, difficulties with thinking and mood problems in Veterans with GWI "	68 veterans deployed in GW meeting criteria Kansas and CDC criteria for GWI 2000mg Resveratrol for 6 weeks (following titration from 500mg in 500mg increments every 6 weeks) vs identical placebo	Kansas and CDC	1°: Cognitive function (CVLT-II), mood (BDI-II), and daily functioning (WHODAS 2.0) 2°: hippocampus scans (MRI and DTI) Time frame: baseline and 26 weeks
Ubiquinol[55] NCT02865460 RCT VA Office of Research and Development; VA Miami, Boston, Minneapolis, and Bronx Health Care Systems	CoQ10 in Gulf War Illness	Recruiting as of Oct 2019; E: Sept 30, 2020	"determine if treatment with ubiquinol improves the physical function of men and women Veterans suffering from GWI"	200 GWV who were in good health prior to 1990. currently with moderate-severe GWI Ubiquinol: 2x200mg for 2 months; 1x200mg for 4 months vs placebo	Kansas	1°: SF-36 every 4 wks to 28 wks 2°: Fatigue (MFI), GWI symptoms, pain (BPI), Sleep (PSQI), anxiety (HAM-A), physical activity (FitBit), trauma (DTS), cognitive symptoms (CPT-3), recall and memory (CVLT-II), visual memory (BVMT), GWI associated blood biomarkers (CBC), depression (HAM-D), circadian rhythm (cortisol levels through saliva), thyroid status (HPT axis levels), HPG axis levels
Visbiome vs VSL#3[56] NCT03078530 RCT Ashok Tuteja; DoD VAMC Salt Lake City, UT	Probiotic (Visbiome) for Gulf War Illness	Recruiting as of Dec 2017; E: May 31, 2018	"determine whether Visbiome will improve intestinal symptoms of IBS and non-intestinal symptoms (fatigue, joint pain, insomnia, general stiffness and headache) associated with IBS"	60 GW Veterans with IBS and 2 or more non-intestinal symptoms > 6 months Three arms: Visbiome vs VSL#3 vs placebo	Not specified	1°: IBS-related symptoms (BSS at 8 weeks) 2°: chronic fatigue (1-5 scale; Baseline to 4 and 8 weeks)
Other						
Electrical stimulation (stochastic noise)[57,70] Proposal: GW130093	Use of a Portable Stimulator to Treat GWI	Completed; poster presented at Neuroscience Nov 2018.	“We hypothesize that stimulation of the vestibular system with electrical stochastic noise via surface electrodes will produce immediate and	60 GW Veterans with GWI and vestibular loss Stochastic noise electrical stimulation vs sham electrical	Not specified	1°: Ocular torsion; sway; balance; dizziness

Intervention; Registration; Study Design; Sponsors; Setting	Study Title	Status; completion date	Purpose of study	Participants; Intervention(s)/ Comparator	GWI case definition	Outcome(s) and timing
DoD CDMRP; Rutgers, Newark, NJ		Results shown in Table 14	long-term improvements in vestibular function and balance."	stimulation bilaterally through ear clips for 12 weeks		
LED therapy[58] NCT01782378 Crossover RCT VA ORD; VA San Francisco and Boston	Scalp Application of Red and Near-Infrared Light, From Light-Emitting Diodes (LED) to Improve Thinking and Memory in Veterans with Gulf War Illnesses	Active - not recruiting. Mar 2019. Results submitted; E: December 31, 2019	"learn if an experimental [LED] treatment can help thinking ability, and memory in Veterans with Gulf War Veterans Illnesses (GWVI)"	160 GW Veterans meeting CDC and Kansas criteria, and with neuropsychological symptoms Real LED Treatment Series First vs Sham LED Treatment Series First. 15 sessions with helmet (real or sham) and intranasal devices	CDC and Kansas	1°: Attention/Executive Function (Stroop Test) 2°: Additional Attention/Executive Function (WAIS-IV and D-KEF); learning and memory (CVLT-II); Mood (BDI); SF-36 physical; blood tests: mitochondrial function, inflammation, coagulation
Nasal Irrigation (Xylitol vs saline)[59,60] NCT01700725 RCT University of Wisconsin, Madison	Effectiveness of nasal irrigation for chronic rhinosinusitis and fatigue in patients with Gulf War illness: protocol for a randomized controlled trial	Completed; A: May 2017 Results shown in Table 15	"to determine whether nasal irrigation with Xylitol or saline are effective in the treatment of chronic rhinosinusitis and fatigue symptoms associated with Gulf War Illness"	40 deployed GW Veterans with GWI and chronic rhinosinusitis (CRS) Three arms: Nasal Irrigation (NI) with saline vs NI with xylitol vs usual care	modified Kansas	1°: QoL (SNOT-20) 2°: Fatigue (MFI); HRQoL (SF-36); cost-effectiveness ratio; treatment satisfaction (7-point Likert) Other: laboratory stress- and illness-related biomarkers

*Only analyses of this subpopulation alone would be included for purposes of answering our key questions

Abbreviations: A=Actual; BAC-A=Brief Assessment Checklist for Adolescents; BID=bis in die; BPI=Brief Pain Inventory; BPI-SF=Brief Pain Inventory-Short Form; BSI=Brief Symptom Inventory; BSS=Bowel Symptom Scale; BVMT-R=Brief Visuospatial Memory Test-Revised; CAPS-5=Clinician-Administered PTSD Scale for DSM-5; CBC=Complete Blood Count; CBTi=Cognitive Behavioral Therapy for Insomnia; CDC=Centers for Disease Control and Prevention; CDMRP=Congressionally Directed Medical Research Programs; CDSMP=Chronic Disease Self-Management Program; CFQ11=Chalder Fatigue Scale; CMI=Chronic Multisymptom Illness; CoE=Center of Excellence for Research on Returning War Veterans; CoQ10=Coenzyme Q_{10}; COWAT=Controlled Oral Word Association Test; CPT-3=Conner's Continuous Performance Test - 3rd Edition; CRS=chronic rhinosinusitis; CVLT-II=California Verbal Learning Test Second Edition; DCS=d-cycloserine; D-KEF=Delis-Kaplan Executive Function System; DTI=Diffusion Tensor Imaging; DTS=Davidson Trauma Scale; E=Estimated; EHR=Electronic Health Record; EEG=Electroencephalogram; EMG=Electromyography; ERP=Event Related Potential; FIQR=Revised Fibromyalgia Impact Questionnaire; FIT=Rey 15-Item Test; FODMAP=Fermentable Oligo-, Di-, Mono-saccharides And Polyols; FSS=Fatigue Severity Scale; GI=Gastrointestinal; GW=Gulf War; GWHE=Gulf War Health Education; GWI=Gulf War Illness; GWV=Gulf War Veteran; GWVI=Gulf War Veterans Illness; HA=Headache; HADS=Hospital Anxiety and Depression Scale; HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale; HD-tDCS=High Definition transcranial Direct Current Stimulation; HIT-6=Headache Impact Test; HPG=Hypothalamic-Pituitary-Gonadal; HPT=Hypothalamic–Pituitary–Thyroid; HRQoL=Health-related Quality of Life; HVLT-R=Hopkins Verbal Learning Test – Revised; IBS=Irritable Bowel Syndrome; ISI=Insomnia Severity Index; LDLPFC=Left Dorsolateral Prefrontal Cortex; LED=Light Emitting Diode; LMC=Left Motor Cortex; MAP=Mean Arterial Pressure; MASQ=Mood and Anxiety Symptoms Questionnaire; MBSR=Mindfulness-based Stress Reduction; MCS=Mental Component Summary; MFI-20=Multidimensional Fatigue Inventory-20; MFSI=Multidimensional Fatigue Symptom

Inventory; MPI=Multidimensional Pain Inventory; MPQ=McGill Pain Questionnaire; MRI=Magnetic Resonance Imaging; MRS=Magnetic Resonance Spectroscopy; MSG=Monosodium Glutamate; NI=Nasal Irrigation; NIH=National Institutes of Health; NR=Not Reported; nRCT=non-Randomized Controlled Trial; NSI=Neurobehavioral Symptom Inventory; ORD=Office of Research and Development; PCS=Physical Component Summary; PDI=Pain Disability Index; PFS=Piper Fatigue Scale; PHQ-9=Patient Health Questionnaire 9-item; PHQ-15 Patient Health Questionnaire 15-item; PI=Principal Investigator; preSMA=PreSupplementary Motor Area; PROMIS=Patient Reported Outcomes Measurement Information System; PSQI=Pittsburgh Sleep Quality Index; PTSD=Posttraumatic Stress Disorder; QoL=Quality of Life; rTMS=Repetitive Transcranial Magnetic Stimulation; SCL-90R=Symptom Checklist-90-Revised; SF-12V=Standard Form 12-Veteran Version; SF-36=36-Item Short Form Health Survey; SF-MPQ=Short-Form McGill Pain Questionnaire; SNOT-20: Sinonasal Outcome Test-20; SORT=Semantic Object Retrieval Test; tDCS=Transcranial Direct Current Stimulation; TMT=Trail Making Test; VAMC=Veterans Affairs Medical Center; VAPSHCS=Veterans Affairs Puget Sound Health Care System; VAS=Visual Analog Scale; VNS=Vagus Nerve Stimulation; VSL=Very Safe Lactobacilli; WAIS-IV=Wechsler Adult Intelligence Scale-Fourth Edition; WHODAS=World Health Organization Disability Assessment Schedule

Table 14. Details of single-arm studies of interventions/management strategies for Gulf War Illness

Intervention; Study Design; Sponsors; Setting	Study Title	Purpose of study	Participants; Intervention(s)	GWI case definition(s)	Outcome(s) and timing
Specialized Care Program[29] Single-arm pilot intervention Sponsors not specified: Acknowledgements included - US Army Lieutenant General Ronald R. Blanck Setting not specified	Rehabilitative care of war-related health concerns	"to present SCP data comparing longitudinal health outcomes with baseline health status among a series of Gulf War veterans with persistent symptoms"	109 veterans Specialized Care Program (SCP): 3-week intensive outpatient group program. Medical assessment; collaboration with providers and other GW veterans to develop "symptom-management plan - an individualized combination of regular primary medical care, exercise, self-care, and other active coping strategies"	Not specified	SF-36; Physical symptoms (PRIME-MD patient questionnaire), quality of life, physical health concern (Whitely Index), and psychosocial distress (Somatization, Depression, and Anxiety scales of the BSI) contrasted across time and demographic groups Time frame: SCP entry, exit, and at 1 and 3 months after exit.
Nutrient formula + methylphenidate[50] DoD grant to K-PAX Pharmaceuticals; VA Palo Alto Health Care System, Palo Alto, CA	Treatment for Gulf War Illness (GWI) with KPAX002 (methylphenidate hydrochloride + GWI nutrient formula) in subjects meeting the Kansas case definition: A prospective, open-label trial	“tested the safety, tolerability, and efficacy of KPAX002--a combination of methylphenidate hydrochloride plus a micronutrient formula designed to support mitochondrial function—as a treatment for Gulf War Illness (GWI)”	15 Veterans with GWI GWI Nutrient Formula (4 tablets twice daily) and methylphenidate hydrochloride (5mg twice daily for Week 1 and 10mg twice daily for Week 2-12)	Kansas	1°: Symptoms (GWI SAT; quant scores 0-87) 2°: symptomatology and disability potential (CIS; scores 20-40); fatigue, cognitive symptoms, pain, and sleep problems (0 -100 VAS) Time frame: baseline to Week 12

Abbreviations: BSI=Brief Symptom Inventory; CIS=Checklist Individual Strength; GW=Gulf War; GWI=Gulf War Illness; PRIME-MD=Primary Care Evaluation of Mental Disorders; SAT=Symptoms Assessment Tool; SCP=Specialized Care Program; SF-36=36-Item Short Form Health Survey

Table 15. Available results of unpublished randomized controlled trials of interventions for Gulf War Illness

	Electrical stimulation[57,70]	**Low-glutamate diet**[25,41]	**Xylitol nasal irrigation**[59]	**Yoga**[39,62]
		Descriptive characteristics		
N total	N=60	N=17*	N=40	N=68 (treated)
N per arm	Electrical stimulation (stochastic noise) vs Sham electrical stimulation	Low- vs high-glutamate diet	Saline vs xylitol vs usual care: 14 vs 14 vs 12	Yoga vs CBT: 37 vs 31
Duration of treatment and observation	Tx and Obs: 12 weeks	Tx and Obs: 1 month	Tx: 8 weeks Obs: 26 weeks	Tx: 10 weeks Obs: 6 months
Demographics	NR	12% Female Age: 50 (4)	20% Female Age: 53.8 (SD 7.8) Race: 77.5% non-Hispanic White; 10% White Hispanic; 5% AA/Black; 2.5% Asian; 2.5% Pacific Islander/Hawaiian; 2.5% multiple races Educ: 7.5% high school or less	NR
		Findings (change from baseline), Treatment vs Comparator		
Pain	---		---	**BPI-SF pain** (within group mean ± SD) End-of-treatment **Yoga**: pre- 5.44 ± 2.00 vs post- 4.00 ± 2.08; P < 0.001 **CBT**: pre- 5.09 ± 1.62 vs post- 4.95 ± 2.35; P > 0.05 6-month f/u pain: **Yoga**: 4.70 ± 2.17; P=0.02 **CBT**: NR
Fatigue	---		**MFI score** (mean (SD)): Week 8: Xylitol 0.6 (2.4) vs saline 0.9 (2.3) vs control 0.5 (2.5) Week 26: Xylitol 1.9 (2.8) vs saline -1.4 (2.4) vs control 10.4 (3.0)	---

Mental Health	---	**Anxiety (GAD-7)** (median (IQR))**:** reduced from 9 (13) to 5 (10); P=0.01*	---	---
PTSD	---	**PCL-C score** (median (IQR)): reduced from of 58 (33) to 43 (28); P=0.04*	---	---
Respiratory	---		**SNOT-20 score** (mean (SD)): Week 8: Xylitol -16.9 (4.9) vs saline -8.8 (5.0) vs control -3.4 (5.3) Week 26: Xylitol -18.9 (4.9) vs saline -16.9 (5.3) vs control -3.5 (5.6)	---
Vestibular function	**Ocular torsion (OT):** improved in 53% of pts; mean increases of 25% (range 1-81) **Sway**: improved in 100% of participants; reduced by mean of 42% (Range 21-63).			
Adverse events	NR	NR	No AEs or SAEs	NR

* Preliminary results, study ongoing

Abbreviations: AA=African American; BPI-SF=Brief Pain Inventory-Short Form; CBT=Cognitive Behavioral Therapy; GAD-7=Generalized Anxiety Disorder 7-item; IQR=Interquartile Range; MFI=Multidimensional Fatigue Inventory; NI=Nasal Irrigation; NR=Not Reported; Obs=Observation; PCL-C=PTSD Checklist – Civilian version; PTSD=Posttraumatic Stress Disorder; SAT=Symptoms Assessment Tool; SD=Standard Deviation; SNOT-20: Sinonasal Outcome Test-20

Table 16. Results of single-arm studies of interventions/management strategies for Gulf War Illness

Intervention	Specialized Care Program[29] (Multicomponent group program)[a]	KPAX002[50] (Nutrient formula plus methylphenidate)
Descriptive characteristics		
Total N	N=109	N=15
Duration of treatment and total observation	Tx: 3 weeks Obs: 1 & 3 months	Tx and Obs: 12 weeks
Demographics	18.3% Female Age: 56% younger than 40 years of age Race: 50.5% White; 30.3% Black; 19.3% Others	12% Female Age: 53.0 (6.15) Race: 12% AA/Black, 6% Hispanic, 6% Native American, 71% white, 6% other
Findings (mean difference from baseline)		
Physical Health Overall	**SF-36 PCS** End-of-treatment (N=93): 1.08 (P=NS) 1-mo f/u (N=48): 0.96 (P=NS) 3-mo f/u (N=37): 1.49 (P=NS) **No. of physical symptoms** End-of-treatment (N=102): -2.54 (P < 0.01) 1-mo f/u (N=51): -0.80 (0.01 < P < 0.05) 3-mo f/u (N=37): -1.14 (0.01 < P < 0.05)	---
Fatigue	---	**CIS**: -14 (±19.59) 95% CI, −22.3 to −5.7; P < 0.001 **VAS**: -1.3 (±2.41); P=0.019
GWI Symptoms Overall	---	**SAT**: -8.8 (±12.54); 95% CI −13.2 to −4.5; P < 0.001
Mental Health Overall	**SF-36 MCS** End-of-treatment (N=93): 5.17 (P < 0.01) 1-mo f/u (N=48): -0.69 (P=NS) 3-mo f/u (N=37): 0.70 (P= NS) **Physical Health Concern (Whitely Index score):** End-of-treatment (N=97): -0.65 (0.01 < P < 0.05) 1-mo f/u (N=49): -0.78 (P=NS) 3-mo f/u (N=37): -1.41 (P < 0.01)	---
Psychosocial distress	**Somatization score** (**BSI)** End-of-treatment (N=97): -4.75 (P < 0.01) 1-mo f/u (N=49): -2.77 (P=NS) 3-mo f/u (N=37): -7.74 (0.01 < P < 0.05) **Depression score** (**BSI**) End-of-treatment (N=97): -3.05 (0.01 < P < 0.05) 1-mo f/u (N=49): 1.96 (P=NS) 3-mof/u (N=37): 1.38 (P=NS) **Anxiety Score** (**BSI**) End-of-treatment (N=97): -3.52 (P < 0.01) 1-mo f/u (N=49): -1.19 (P=NS) 3-mo f/u (N=37): -2.90 (P=NS)	---
Other	---	**Sleep VAS**: -1.4 (±2.47); P=0.026 **Pain VAS**: -1 (±2.62); P=0.054 **Cognitive**

Intervention	Specialized Care Program[29] (Multicomponent group program)[a]	KPAX002[50] (Nutrient formula plus methylphenidate)
		disturbance VAS: -1.5 (±2.45); P=0.006
Severe AEs/ dropouts due to AEs	---	No SAEs; 2 dropouts due to AEs

[a] An intensive outpatient program that included medical assessment and collaboration with providers and other GW Veterans in the development of an individualized symptom management plan combining primary medical care with exercise, self-care, and other active coping strategies.

Abbreviations: AA=African American; AE=Adverse Event; BSI=Brief Symptom Inventory; CIS=Checklist Individual Strength; F/U=Follow-up; MCS=Mental Component Summary; NS=Not Significant; P=P-value; PCS=Physical Component Summary; SAE=Severe Adverse Event; SAT=Symptoms Assessment Tool; SCP=Specialized Care Program; SF-36=36-Item Short Form Health Survey; Tx=Treatment; VAS=Visual Analog Scale

APPENDIX E. PEER REVIEW COMMENTS/AUTHOR RESPONSES

#	Reviewer Comment	ESP response
Are the objectives, scope, and methods for this review clearly described?		
1	Yes	
2	No - yes they are in sufficient detail	
3	Yes	
4	Yes	
5	Yes	
6	Yes	
8	Yes	
Is there any indication of bias in our synthesis of the evidence?		
1	No	
2	No	
3	No	
4	No	
5	Yes - the review seems to be done fairly, and in an unbiased way	
6	No	
8	No	
Are there any published or unpublished studies that we may have overlooked?		
1	No	
2	No	
3	No	
4	No	
5	No	
6	No	
8	Yes - Maybe, please see comments in attached review.	
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.		
1	This systematic review of interventions for Gulf War Illness (GWI) was reasonably well done and is timely given the ongoing interest and need for improved management of GWI. I have no concerns or critique of the actual systematic review itself (procedures and write-up) but do have two major concerns, one methodological and the other is more philosophical. First, philosophically I think this review is probably premature. Mainly, because a clinical definition of what GWI remains elusive and there is no consensus or diagnostic definition. As a consequence, this review is really nothing more than a review some treatments for diseases that may (or may not) be part of a more "global" disease/disorder that we refer to as GWI. Until	We agree that there are many challenges inherent in the study of an illness that is poorly defined. We do cite some of these limitations in the discussion section. Our hope and goal was to identify treatments that might be promising and worthy of further inquiry as well as identify treatments that may be ineffective or harmful. We have modified our aim to clarify this point.

#	Reviewer Comment	ESP response
	such time that we get to consensus agreement on exactly what GWI is and what diseases/disorders/symptoms define GWI we doing nothing more than "guessing" about managing GWI by using treatments for specific diseases/disorders that we "believe" are part of GWI and may have shown efficacy in the past, and hoping that they work similarly in those we define as GWI by the CDC/Kansas definition.	
1	Which brings me to my second major concern. In the Executive Summary (pg. 1) and in the "Study Section" (pg. 10) you state that: "We excluded studies that compared interventions in Veterans with versus those without GWI.". I believe that exclusion of these types of studies is a catastrophic limitation to this report for several reasons. One, relates to the concern raised above in that, since we do not have a clinical definition/criteria to define/diagnose GWI (other than CDC & Kansas criteria) we really do not know what we are dealing with. Thus, the treatments evaluated are not treatments for GWI, but rather for specific other diseases/disorders that may, or may not, be part of the GWI. It would have been inherently interesting and informative to have included studies that compared GWI versus no GWI. If for example, those designated as GWI (by CDC/Kansas) failed to show a favorable response to CBT or CPAP compared to those without GWI would suggest that simply using existing treatments/interventions for the symptom domains of GWI is not effective and that at present we have a great deal of work yet to do to develop treatments/interventions in and for GWI. By not including the non-GWI comparative studies we have limited information as to whether the treatments/interventions evaluated in this review work as well for the target disorder/symptom domain in those with GWI.	All of the studies compared treatment and placebo in a cohort of Veterans who were identified to have GWI. We did not exclude any studies for including a population other than GWI (and we were open to the possibility of including such as study had they met all of our other inclusion criteria e.g., also included a control group with GWI). We have revised the Study Selection section to be clear that we would have included studies that compare the same intervention in GWI and another illness as long as that study also had a control treatment had we found any.
1	Since one of the purposes of this type of review is to summarize a literature with aim of providing some clinical guidance regarding best practice. That aim was not achieved, in part due to the wide variability in the science, lack of a consensus clinical definition of GWI, and exclusion of studies that employed non-GWI comparison group. Until such time that a clinical diagnostic criteria is ratified, the within and between groups variability will never afford the stability necessary to generate meaningful information from systematic reviews.	We agree that there are many challenges inherent in the study (and evidence synthesis) of an illness that is poorly defined. We do cite some of these limitations in the discussion section. We clarify that our aim was not to characterize literature in the spirit of developing treatment guidelines, rather we sought to identify treatments that might be promising and worthy of further inquiry as well as to identify treatments that may be ineffective or harmful. This would help streamline future resources to build an evidence base to develop clinical guidelines. The use of the report would be up to the stakeholders.

#	Reviewer Comment	ESP response
1	Research with an emphasis on defining GWI is paramount. Fortunately, there are two such studies, currently in their first year, underway. One is using a comprehensive chart review process to better understand the clinical manifestations in those with presumed GWI and the other is employing a "machine learning" approach mining VHA healthcare data to try and identify clusters of healthcare data that may correlate with clinical classifications of GWI.	Thank you for this information. We have now specifically referenced these ongoing studies in the discussion section.
1	This systematic review was done with rigor and is well written however, for the reasons noted above, I believe it is premature and offers clinicians little with regard to management of their patients with believed to be suffering with GWI.	Thank you, we have clarified in our Aims that our goal was not to develop clinical guidelines rather to review current evidence to (1) identify treatments that might be promising and worthy of further inquiry and (2) identify treatments that may be ineffective or harmful.
2	This is extremely well done and will prove very valuable. I have no concerns. While there may be other studies out there, they are not of major importance or relevance.	Noted, thank you.
3	Thank you for the opportunity to review this evidence based synthesis. I read this over a few times and had very few comments. This was excellently done, easy to read and clear. Thank you. I had one main comment. I think the reviewers should include information on adherence. Adherence to these treatments were generally low. I know that this wasn't a primary purpose of the study – but it would be easy to include it in the tables and I think it would be informative. If a Veteran won't use the treatment, this is important to know.	We agree this is important, especially when considering feasibility of patient engagement in psychosocial and exercise interventions that are time intensive. We have now added information about adherence for all studies that reported it.
3	Minor comment: First table – what does PTSD mean in the label for the table under mindfulness?	This was originally to display a subpopulation that was examined in the study, we have removed it to reduce confusion.
4	I think that this is an excellent review. Well done.	Thank you.
	Page 25: I would comment on the Study of Amin et al. on the use of CPAP in GWI and sleep disordered breathing. DOI 10.1007/s11325-010-0406-8.(12) This study of GWI and sleep disordered breathing (SDB) appears to confirm the effectiveness of nasal CPAP in treating the symptoms of SDB and obstructive sleep apnea. According to the AASM criteria, as listed in the International Classification of Sleep Disorders: Diagnostic and Coding Manual, Second Edition. At least 1 of the following criteria must apply for obstructive sleep apnea (OSA) to be diagnosed: • The patient reports daytime sleepiness, unrefreshing sleep, fatigue, insomnia, and/or unintentional sleep episodes during wakefulness. The patient awakens with breath holding, gasping, or choking. The patient's bed partner reports loud snoring, breathing interruptions, or both during the patient's sleep.	This is a valid point. CPAP is an evidence-based treatment used to treat sleep apnea. The patients in the study all had sleep-disordered breathing in addition to GWI. We think this intervention is important to include because the study found improvement in broader range of GWI symptoms (not just sleep outcomes) with CPAP treatment. It therefore may be worthwhile for clinicians to determine whether Veterans with GWI have sleep-disordered breathing and use a CPAP to address both sleep disordered breathing as well as a broader range of GWI symptoms.

#	Reviewer Comment	ESP response
	• Polysomnography (PSG) shows more than 5 scoreable respiratory events (eg, apneas, hypopneas, RERAs) per hour of sleep and/or evidence of respiratory effort during all or a portion of each respiratory event. • PSG shows more than 15 scorable respiratory events (eg, apneas, hypopneas, RERAs) per hour of sleep and/or evidence of respiratory effort during all or a portion of each respiratory event. • Another current sleep disorder, medical or neurologic disorder, medication use, or substance use does not better account for the patient's condition. Many of the GW Veterans included in this study fit the OSA criteria; it is not a surprise that symptoms improved with CPAP. I don't think this study adds valuable knowledge about treatment of GWI. This study uses an evidence-based intervention, CPAP, to treat SDB/OSA. The patients in this study had symptoms that were readily attributed to a diagnosable condition other than to GWI, that is OSA. I think your review should provide this information in your discussion of the study results. It is a source of bias in the study.	
5	Overall I found the Evidence Synthesis Program to be a very well organized review of a complex literature. I think it will be a valuable resource for those working in the field of Gulf War Illness. Specific comments follow;	Thank you. See responses below.
	p. 23 line 11: typo "delivered a in 8 weekly…" should read "delivered in 8 weekly…"	Corrected.
	p.23, line 41 states that participants used self-reported outcomes without blinding of participants. Since blinding of participants is not possible in psychological and exercise interventions, I suggest clarifying the statement to say this.	The role and necessity of patient blinding in studies of these types of interventions has been debated. There are techniques even for complex nonpharmacologic interventions to blind patients to some degree. Some argue that lack of patient blinding in trials of non-pharmacologic therapies may considerably exaggerate treatment effects; in which case, it would be difficult to determine whether and to what extent positive treatment effects – especially for the findings with only low level confidence – were due to an independent effect of treatment, expectancy as a mechanism of change, placebo effect, or a combination of these factors. On the other hand, others have argued that blinding is not only challenging but also potentially counterproductive as expectancy for change is thought to be an integral part of the intervention itself. We have added this to the discussion.

#	Reviewer Comment	ESP response
	p. 29, line 35 describes the study done by my group (I am the P.I.). The manuscript giving details of the study and the results is still under peer review, and is described in the Evidence Synthesis Program using ref #37 (clinicaltrials.gov identifier) and ref #58 (an abstract). The information from these references is incomplete. I don't know if the manuscripts will be excepted for puplication before the Evidence Synthesis Program is published, here is the reference for the manuscript currently under review. Bayley, P. J., Cho, R. Schulz-Heik, R. J., Mathersul, D. C., Collery L., Shankar, K. Ashford, J. W. Jennings, J. Tang, J. Wong, M. Avery, T. J. Stanton, M. Meyer, H. Friedman, M. Kim, S. Jo, B. Younger, J. Mathews B., Majmundar M. & Mahoney L. Yoga is effective in treating symptoms of gulf war illness: a randomized clinical trial (in review). I do not want to list all the results in the paper before it is published, but you may want to cite it (e.g., p.29, in the paragraph starting on line 35). For accuracy, I suggest making the following edits to the existing text; i. The comparator group in the study is more accurately described as CBT. I recommend changing Table 7 the comparator group from a "pain management wellness group" to "CBT". Similarly, p.29, line 35 should refer to a "CBT" group rather than a "CBT-based pain management wellness group for pain". Similarly, p. 69 line 24-25 "pain management wellness group" should be changed to "CBT" ii. the study used the CDC GWI case definition, so I suggest changing p.68, line 56 from "not specified" to "CDC"	We have made these changes as suggested.
	p. 33, line 45 refers to publication #4 as "a narrative review of …GWI research". It doesn't look like a review to me, and the abstract calls it "a double-blind, placebo-controlled study".	Thank you, that citation was incorrect. We have replaced it with the correct citation: Chester JE, Rowneki M, Van Doren W, Helmer DA. Progression of intervention-focused research for Gulf War illness. *Mil Med Res.* 2019;6(1):31.
	The Summary Table (p.36-37) describes the results from a large RCT by Donta et al (2003). The table shows the results for the CBT (line 54) and CBT + Exercise (line 56) interventions, coded to show evidence of benefit for pain. I am not sure this is accurate. Donta et al stated that "only 1 of the 4 measures of pain (affective) showed significant treatment differences for CBT alone and CBT plus exercise compared with usual care" As a result, Donta et al state several times that "neither treatment had a significant impact on pain" (Abstract, Comment). In my opinion, it would be more accurate to recode the findings for pain in this study to be either Mixed/Unclear (which would then match how they are reported in Table 5), or even No Benefit.	Thank you for pointing out this discrepancy between tables. We meant for it to be mixed/unclear findings for CBT and CBT+Exercise for pain and have updated the summary table to reflect this.

#	Reviewer Comment	ESP response
8	Overall, this manuscript provides a comprehensive National overview of published and currently active Gulf War studies with focus on treatments and therapeutics. Inclusion of Risk of Bias (ROB), Strength of Evidence (SOE), and discussion of studies focused on GWI vs. symptoms of GWI are strengths of this review. This manuscript will no doubt provide important Gulf War field-forward objectives and guidance for investigators and funding agencies.	Noted, thank you.
	Could the authors include a paragraph or discussion of a Standard Operation Procedure (SOP) or an outline of how clinical trials should be experimentally and methodologically assembled for subsequent good synthesis review? This could be a nice value added to this manuscript as VA often contracts with NASEM and inclusion of studies are important for overall interpretation.	This is a very important point, but it is beyond the scope of this report. We have asked the ESP Coordinating Center to examine this issue and have had follow up correspondence about a plan to help develop some guidance about this. We also include in our discussion very broad points about future research needs and approaches, but these are by no means comprehensive.
	Could the authors include a discussion of literature not included in the ESP that maybe a promising treatment on the horizon if the experimental approach were solid.	Unfortunately, for the systematic review, we are only able to include literature captured by our search and that meets our inclusion criteria. Key Question 3 does capture ongoing studies of treatments, but anything beyond that is outside the scope of this review.
	Executive Summary (pg1) …We excluded studies that compared interventions in Veterans with versus without GWI… why? Were there treated and untreated numbers in each group? If so, wouldn't that include GWI Veterans with and without treatment?	We have clarified that this exclusion would only be in the case where both treated and untreated groups contained GWI and non-GWI participants, and there was no separate analysis. However, no studies were excluded for this reason.
	Executive Summary (pg1): Were there any nRCTs in the literature and considered or not for evidence synthesis?	The study design was allowed, but none met our inclusion criteria, with the exception of one ongoing study on acupressure (see Table 13).
	Executive Summary (pg1) MBSR, MBB, and CPAP results: "improved" outcomes including fatigue, depression, PTSD, pain cognitive, and sleep. How was improved defined? Was this a qualitative conclusion by the authors or was it based on objective quantitative measures?	We are trying to be brief in the Executive Summary, but we have added a footnote referring readers to the full report for how improvement was defined in the relevant studies.
	Abbreviations Table (pg4) Please add: •AE = Adverse Effect •PICOTS = ? •SOE = Strength of Evidence	We have made the suggested changes.
	Evidence Report (pg8) Introduction: •Add symptoms within 6-month deployment were applicable	We have added this in the introduction.

#	Reviewer Comment	ESP response
	Methods (pg9) Figure 1. Conceptual Framework We may need to tweak this figure. Suggestions: • Remove “case definition” under Patient Subgroups. There is no clinical case definition. • Remove “case definition” under Veterans with GWI. Include: … and meet inclusion/exclusion criteria based on the instrument.	Thank you, we have made this change to the Figure 1.
	Study Selection (pg10): We excluded studies that compared interventions in Veterans with versus Veterans without GWI: How many studies were excluded?	We did not count how many were excluded for this exact reason, but they would fall under “excluded populations” in our full text review (see literature flow diagram). Since there were 5 exclusions for population, there are 5 or less studies that were excluded for this reason.
	Table 1 PICOTS by Key Question (pg 11): Key Question (KQ2 – hard to understand based on current wording. Please rephrase.	We have edited the wording of the question for clarity.
	Data Abstraction, Quality Assessment (pg12): In lieu of “investigator” or reviewer(s), Consider changing to ESP-reviewing member or ESP-reviewer where applicable.	We have made this change.
	Quality Assessment: ROB should be on the first sentence, not sentence 2.	Correction made.
	Table 3. (pg21). Table 4 (pg22): Remove ROB after low, high.	Correction made.

= anonymous reviewer number