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

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

Operational Partners

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

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Technical Expert Panel (TEP)

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

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Peer Reviewers

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

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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.

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:

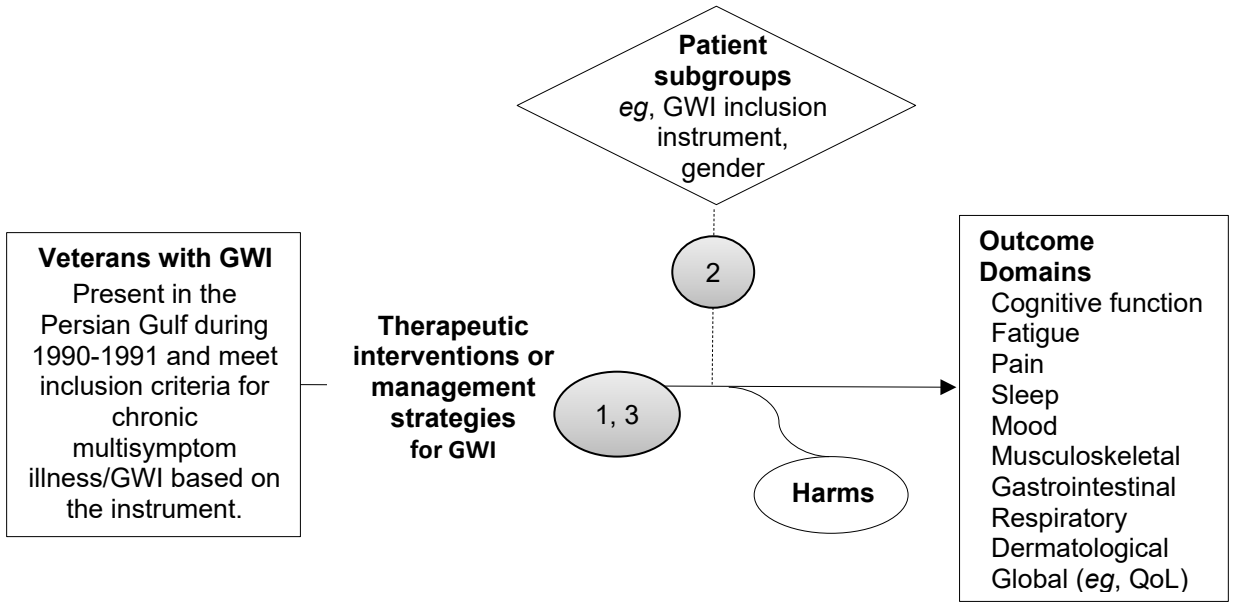
1. Evidence on effectiveness/harms: What are the benefits and harms of pharmacological and non-pharmacological interventions and management strategies for Veterans with GWI?

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

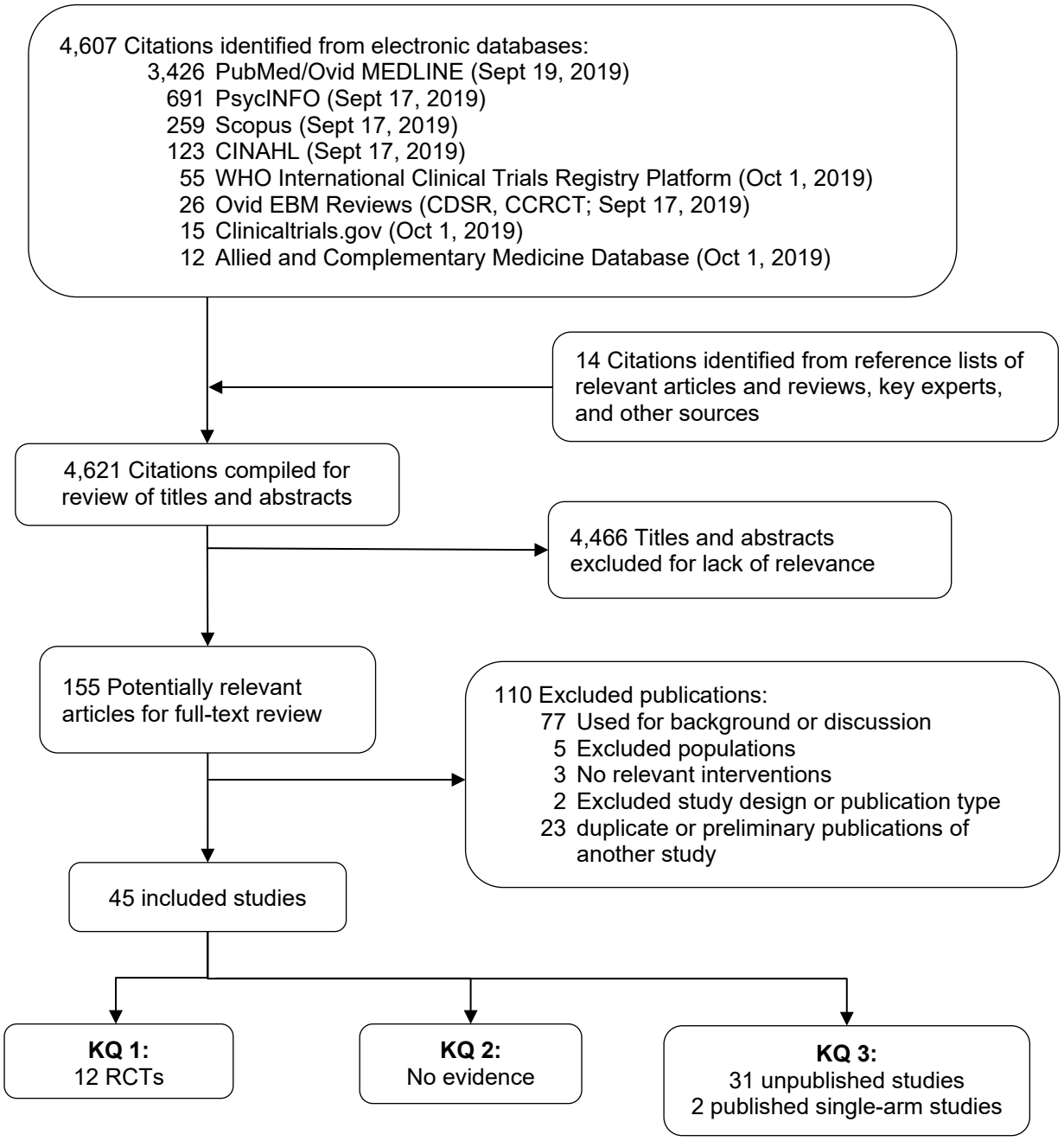
We assessed the overall strength of evidence (SOE) for each outcome using a method developed for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPCs).[21] The AHRQ EPC method considers study limitations, directness, consistency, precision, and reporting bias 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 D, 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.

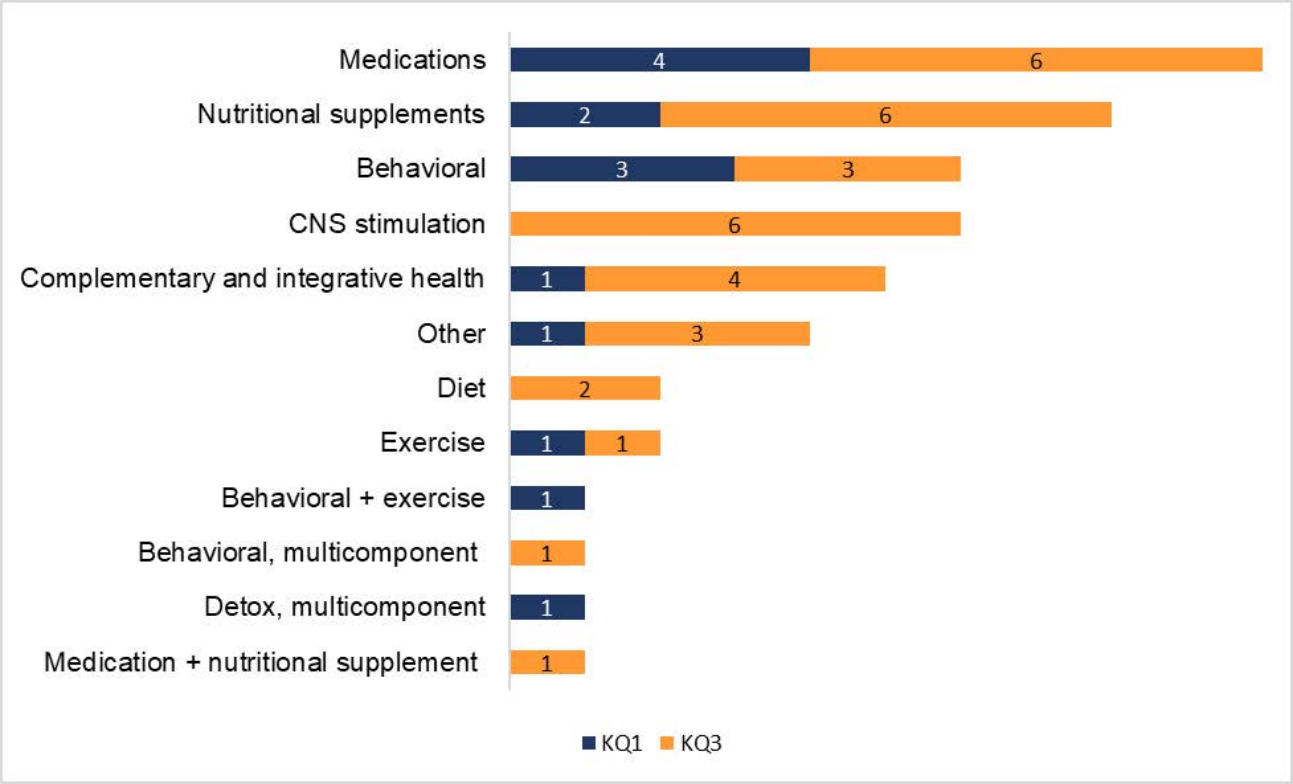
DISCUSSION

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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