

Treatment Research In Gulf War Illness Discussion

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Treatments for GWI

- To date, there are no known effective treatments for GWI or for its specific symptoms that have been scientifically validated.
- Identifying viable treatments is a top priority but has been slow due to incomplete understanding of the pathobiology of the illness and previous lack of treatment as a priority in funding.
- However, a surge of treatment trials has been funded in the past 5 years.
- Results from these studies are now starting to be published.

Published Treatment Trials for GWI from 2009-2013

Amin et al, 2011

- Randomized double blind control trial of CPAP in 17 Male GWV with GWI and sleep disordered breathing
- Therapeutic CPAP improved pain, fatigue, cognitive function, sleep quality, and reported physical and mental health; Sham CPAP not effective

Conboy et al, 2012

- Randomized waitlist control trial of Acupuncture in GWV with GWI
- Indicated positive initial results
- Final grant report showed acupuncture group had higher scores on SF36 and decreased McGill pain scores post-treatment.

Erickson, Golomb et al, 2013

- Double blind placebo controlled crossover trial of Co-Q10 in GWV with GWI
- Indicated positive initial results

Baraniuk, Rayhan et al, 2013

- Randomized double blind placebo controlled pilot study of Carnosine in 25 GWV with GWI Carnosine improved on the WAIS-R digit symbol substitution test, an improvement in irritable bowel syndrome symptoms, specifically diarrhea
- No changes were seen in the placebo group

GWV Treatment Approaches

Treatments for GWV can be symptom-based or focus on proposed illness mechanisms. It is likely that both approaches to treatment are necessary to most quickly identify an effective treatment(s).

Examples of symptom-based and mechanism based therapies were presented at recent Committee meetings.



GWl Treatment Approaches

Symptom based treatments

- Acupuncture, continuous positive airway pressure (CPAP) for sleep difficulties, and exercise resistance training, pain medications, mindfulness and nutraceuticals for pain management

Mechanism based treatments

-glial modulators, innate immune modulators, anti-inflammatories, antioxidants and axonal transport stabilizers as single interventions for multiple GWl symptoms, including fatigue, cognitive complaints and chronic pain. Specific treatments include:

- Low Dose Naltrexone (LDN)
- Mifepristone
- Carnosine
- Co-enzyme Q10



GWl Treatment Approaches

•As pathobiological mechanisms of GWl have been hypothesized, more mechanistically based treatment trials have been conducted.

•Specific treatments for neuroinflammation, oxidative stress, and neuroendocrine alterations have been funded.

•This focus is promising given the lasting effects of neurotoxicant exposure on mitochondrial functions, neuroendocrine function and neuroinflammatory processes shown in animal models.



Currently Funded Symptom-Based Treatments for GWI

Investigator	Funding Source	Treatment	Group	Design/Method
Cook	VA	Exercise Resistance Training	GWV with chronic musculoskeletal pain	Randomized waitlist control trial
Kearney & Hunt	VA	Mindfulness	GWV with GWI	Randomized control trial
Lin	VA	Antibiotic	GWV with IBS	Randomized control trial
Ashford	VA	rTMS	GWV with chronic pain	Randomized control trial

Currently Funded Symptom-Based Treatments for GWI

Investigator	Funding Source	Treatment	Group	Design/Method
Conboy	CDMRP	Acupuncture	GWV with GWI	Randomized waitlist control trial
Rabago	CDMRP	Nasal Irrigation	GWV with rhinosinusitis/fatigue	Randomized control trial
Tuteja	CDMRP	Probiotics	GWV with IBS	Randomized control trial
Carpenter	CDMRP	Hubbard detox Program	GWV with GWI	Randomized waitlist control trial
Nakamura	CDMRP	Sleep focused mind-body program	GWV with GWI	Randomized control trial
Lin	CDMRP	Acupressure	GWV with pain/fatigue	Randomized waitlist control

Keys to Developing Mechanistic based therapies

- Identifying mechanistic based therapies and then carefully monitoring of identified biomarkers of illness needs to be done and targeted for mechanism based therapies.
- For example, HPA axis differences have consistently been noted in several studies by Dr. Golier and then she identified a potential therapy to try to reset the HPA axis in GW veterans (mifepristone).



Currently Funded Mechanism-Based Treatments for GWI

Investigator	Funding Source	Treatment	Group	Design/Method
Baraniuk	CDMRP	Carnosine	GWV with GWI	Randomized control trial
Golier	CDMRP	Intranasal Insulin	GWV with GWI	Randomized control trial
Golier	CDMRP	Mifepristone	GWV with GWI	Randomized crossover trial
Golomb	CDMRP	Co-Q10	GWV with GWI	Randomized crossover trial
Meggs	CDMRP	Low Dose Naltrexone	GWV with GWI	Randomized crossover trial
Naeser	VA	LLT	GWV with GWI	Randomized crossover trial

Preclinical Treatment Studies for GWVI

Investigator	Funding Source	Treatment	Animal Group
Abou-Donia	CDMRP	Flupirtine	Rats
O'Callaghan	CDMRP	Minocycline	mice
Ait-Ghezala	CDMRP	Genetic and pharmacological modulators	mice
Shetty	VA	Antidepressants, Antioxidants, and exercise	Rats

Summary

GWVI treatment research has focused on both symptom based and mechanistic based approaches.

Most clinical treatment trials are currently ongoing and results are not yet available for review

- The VA is currently funding 5
- CDMRP is currently funding 11

Several current animal model studies are currently ongoing and will provide proof-of-concept to determine if human trials are warranted

- The VA is currently funding 1
- CDMRP is currently funding 3

Discussion

- New Ideas/avenues for treatment?
 - Flavonoids to reduce neuroinflammation and improve mitochondrial function (quercetin, luteolin)
 - Glial modulators to reduce neuroinflammation
 - Other pharmaceuticals
 - Complementary/Integrative therapies:
 - Tai Chi
 - Laser acupuncture
 - Yoga nidra



Flavonoids to improve neuroinflammation and mitochondrial functioning

- Quercetin and luteolin are naturally occurring polyphenolic flavonoids found in apples, onions, celery and green peppers.
- They have antioxidant and anti-inflammatory properties thought to improve mitochondrial functioning and reduce neuroinflammation. Two of the commonly hypothesized mechanisms for GW illness.

Panel Discussion

1. What are the most promising Scientific Treatments to develop?
2. What is the best process to develop new treatment ideas?

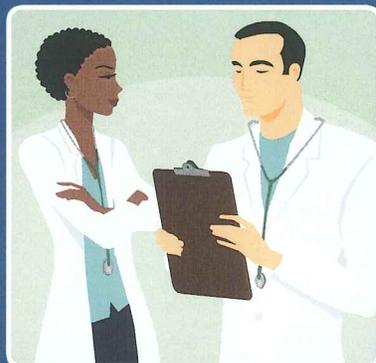


Other Treatment Issues for Discussion

- All treatment trials should use consistent case definition criteria for comparability of results
- GW veterans and practitioners should be surveyed regarding what treatments are helpful, not helpful or may make symptoms worse
- Should clear goals for number of treatments be set to ensure more clinical trials are being funded?
- Should more pilot studies be encouraged?



Discussion



Panel Speakers

William Meggs

Julia Golier

Rakib Rayhan

Jim O'Callaghan

Fiona Crawford

ANIMAL MODELS OF GWI

- Direct examination of the brain tissue is a key advantage
- Persistent molecular, cellular and functional effects associated with individual and combined exposures/conditions encountered in the Gulf War can be evaluated
- Specific hypotheses can be tested
- Therapeutic interventions can be evaluated

NEUROINFLAMMATION MODEL OF GWI

- Diisopropyl fluorophosphate (DFP), used as sarin surrogate, unexpectedly causes brain “neuroinflammation”; effects consistent with “sickness” behavior in a mouse model.
- The anti-inflammatory rodent stress hormone, corticosterone (CORT), even more unexpectedly, makes DFP neuroinflammation markedly worse
- Taken together, these observations led to a neuroinflammation model of GWI based on combined exposure to physiological stress and nerve agent
- Specific hypotheses can be tested
- Therapeutic interventions can be evaluated

MINOCYCLINE AS A THERAPEUTIC AGENT IN THE MOUSE NEUROINFLAMMATION MODEL OF GWI

- Minocycline: Tetracycline type antibiotic; been in man for 30 years; very well tolerated
- Has strong anti-inflammatory effects against multiple animal models of inflammation and in man
- Marked suppression of neuroinflammatory mediators in two mouse models of neurotoxicity with neuroinflammatory components (METH and MPTP)
- Minocycline failed in large ALS clinical trial: not unexpected; it's anti-inflammatory, not necessarily neuroprotective/neuroregenerative

WHAT DID WE FIND WITH MINOCYCLINE?

- Suppresses some but not all mediators of neuroinflammation in our GWI mouse model
 - Early time points only
 - Multiple brain regions (and other tissues)
 - Serum inflammatory marker data under analyses
- When PB/DEET are added to CORT and DFP, neuroinflammation is not worse but the anti-inflammatory effects of minocycline are diminished.