

Presentation 8 – Lea Steele

**Research on Treatments for Gulf War
Veterans' Illnesses:
Background and Context**

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GWI Treatment Research

- Challenges of studying GWI treatments
- Evaluating evidence re: treatment effects
- VA/DOD Clinical Practice Guidelines
- Treatment studies of GWI
- Identifying "new" treatments

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GWI Treatment Research

- Treatment Information we've discussed
 - > ABT, EBT Clinical Trials
 - > VA/DOD Clinical Practice Guidelines
 - > Clinical experience at NJ WRIISC

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GWI Treatment Research

Evaluating GWI treatments is extremely challenging

- > GWI may include multiple pathophysiological processes
 - May require treating concurrent problems that differ in different people
 - Which subgroups benefit from which treatments?
- > No objective clinical markers of illness
- > No accepted GWI case definition
 - Who has Gulf War illness/who does not?
- > How best to measure health improvement/response to treatments?

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GWV Treatment Research

- **Measuring Improvement: Outcome Measures**
 - > Change/elimination of biological indicator of pathology (e.g. infection)
 - > Sustained symptom improvement
 - > Improvements in functional status on standardized tests
 - SF-36, SIP, cognitive function, etc.
 - Exercise tolerance

GWV Treatment Research: Measuring Outcomes

- **SF-36**
 - > Evaluates health/functional status in several domains of daily life
 - Physical function summary score (PCS)
 - Mental health function summary score (MCS)
 - > Mean score in the general population is 50 (scale of 0-100)
 - > Mean scores associated with diseases:
 - Diabetes = 42
 - COPD = 36
 - GWV participants in ABT trial = 30

Evaluating Evidence of Treatment Efficacy; Effectiveness

Levels of Evidence (IOM, 2001)

- Level
- 1 Multiple well-designed RCTs; multiple well-designed outcomes studies
 - 2 Single well-designed RCT; single well-designed outcomes study
 - 3 Consistent findings from multiple observational studies
 - 4 Single cohort or case/control observational study
 - 5 Unsystematic observation, expert opinion, consensus judgment

Gulf War Veterans' Illnesses: Treating Symptoms and Syndromes. IOM, 2001

GWV Treatment Research: Little Evidence to Evaluate

- **VA/DOD Clinical Practice Guidelines: Recommendations of Expert Panels**
 - > Post Deployment Health Concerns
 - > Medically Unexplained Fatigue and Pain
- **VA/DOD Clinical Trials**
 - > EBT
 - > ABT

VA/DOD Clinical Practice Guidelines: Medically Unexpl Fatigue and Pain

VAND CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF MEDICALLY UNEXPLAINED SYMPTOMS (MUS), CHRONIC PAIN AND FATIGUE
Guideline Summary

PRIMARY CARE

GUIDELINE SUMMARY

- Establish that the patient has MUS.
- Obtain a thorough medical history, physical examination, and medical record review.
- Minimize low-yield diagnostic testing.
- Identify treatable cause (condition) for the patient's symptoms.
- Determine if the patient can be classified as Chronic Multi-Symptom Illness (CMI) (i.e., has two or more symptoms: chronic pain, fatigue, cognitive dysfunction, or sleep disturbance).
- Negotiate treatment options and establish collaboration with the patient.
- Provide appropriate patient and family education.
- Maximize the use of non-pharmacologic therapies:
 - Graded aerobic exercise with close monitoring.
 - Cognitive behavioral therapy (CBT).
- Empower patients to take an active role in their recovery.

VA issues a full guideline. This document is a high-priority summary. May 2002. Copyright © 2002 by the Department of Veterans Affairs. All rights reserved. This document is available at: <http://www.va.gov/wharton/wharton.htm>

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Clinical Practice Guidelines: Medically Unexplained Fatigue and Pain

THERAPY INTERVENTIONS FOR FIBROMYALGIA

Intervention	Strongly Supportive	Supportive	Weakly Supportive	Not Supportive
A. Cognitive Behavioral Therapy (CBT) + Graded Aerobic Exercise + Antidepressant (SSRI)				
B. CBT + Graded Aerobic Exercise + Antidepressant (SSRI) + NSAID (or NSAID)				
C. Graded Aerobic Exercise + Antidepressant (SSRI) + NSAID (or NSAID) + Cognitive Behavioral Therapy (CBT)				
D. Graded Aerobic Exercise + Antidepressant (SSRI) + NSAID (or NSAID)				

THERAPY INTERVENTIONS FOR CFS

Intervention	Strongly Supportive	Supportive	Weakly Supportive	Not Supportive
A. Cognitive Behavioral Therapy (CBT) + Graded Aerobic Exercise				
B. Graded Aerobic Exercise + Antidepressant (SSRI) + NSAID (or NSAID)				
C. Graded Aerobic Exercise + Antidepressant (SSRI) + NSAID (or NSAID) + Cognitive Behavioral Therapy (CBT)				
D. Graded Aerobic Exercise + Antidepressant (SSRI) + NSAID (or NSAID)				

Management of Medically Unexplained Symptoms (MUS): Chronic Pain & Fatigue Summary, page 14

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Clinical Practice Guidelines: Medically Unexplained Fatigue and Pain

PHARMACOLOGIC AGENTS FOR CFS/FM*

Agent	Dose/Usual	Effects	Adverse Effects	Comments
Antidepressants	150-300 mg/day (SSRI), 150-300 mg/day (SSRI), 150-300 mg/day (SSRI)	Yes	• Sedation and anticholinergic effects • GI effects	• The agent's antidepressant properties (SSRI) are important. • Tricyclics are not used with caution. • Antidepressants are not used with caution. • Tricyclics are not used with caution.
Antipsychotics	1-4 mg/day	Yes	• Sedation and anticholinergic effects	• Tricyclics are not used with caution.
Anticholinergics	1-4 mg/day	Yes	• Sedation and anticholinergic effects	• Tricyclics are not used with caution.
Antihistamines	1-4 mg/day	Yes	• Sedation and anticholinergic effects	• Tricyclics are not used with caution.
Antiemetics	1-4 mg/day	Yes	• Sedation and anticholinergic effects	• Tricyclics are not used with caution.
Antispasmodics	1-4 mg/day	Yes	• Sedation and anticholinergic effects	• Tricyclics are not used with caution.
Anticonvulsants	1-4 mg/day	Yes	• Sedation and anticholinergic effects	• Tricyclics are not used with caution.
Antiparkinsonian agents	1-4 mg/day	Yes	• Sedation and anticholinergic effects	• Tricyclics are not used with caution.
Antipsychotics	1-4 mg/day	Yes	• Sedation and anticholinergic effects	• Tricyclics are not used with caution.
Antidepressants	1-4 mg/day	Yes	• Sedation and anticholinergic effects	• Tricyclics are not used with caution.
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GWVI Treatment Research: Clinical Trials

EBT: Exercise/Behavioral Therapy Trial

1,092 Gulf War veterans at 20 study sites; 12 mo. therapy

Intervention	SF-36 PCS improved 7 pts. or more	SF-36 PCS mean pts. improved
Usual care	11.5 %	-0.04
Exercise	11.7 %	0.97
CBT	18.5 %	0.59
CBT + exercise	18.4 %	1.03

Management of Medically Unexplained Symptoms (MUS): Chronic Pain & Fatigue Summary, page 14

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GWV Treatment Research: Clinical Trials
ABT: Antibiotic Treatment Trial

491 Gulf War veterans at 26 study sites; 12 mo. doxycycline

	% improved 7 pts. on SF-36	mean SF-36 scores baseline, 12 mos	% mycoplasma neg. @ 18 mos
Doxycycline	18.0 %	30.2 → 32.0	90 %
Placebo	17.3 %	30.1 → 30.9	87 %

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GWV Clinical Trials: No evidence of substantial improvement in veterans' health

- **EBT:**
 - > CBT produced 7% more veterans with 7 pt. SF-36 increase, but less than 1 point mean increase
 - > Exercise/CBT produced some symptomatic improvement
- **ABT:**
 - > Similar % of treatment and placebo group had 7 pt. increase at 12 mos; mean SF-36 increase was ~ 2 points
 - > Mycoplasma infection and GWV?

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Identification of Treatments for GWV: Approaches Used by VA

Levels of Evidence (IOM, 2001)

Level

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GWV Treatment Research: What Next?

- Identifying/evaluating additional GWV treatments
 - > Identification of specific biological mechanisms underlying GWV
 - Use existing treatments that counter those processes
 - Identify new pharmacologic interventions
 - > Systematic evaluation of treatments currently used; investigate claims of treatment success
 - Gulf War illnesses
 - Similar multisymptom conditions

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GWV Treatment Research

- Identifying/evaluating additional GWV treatments:
 - > Identify specific biological mechanisms of GWV
 - > Investigate claims of treatment success

- + Both processes can lead to identification of treatments for evaluation in randomized clinical trials

GWV Treatment Research

- Identifying effective treatments for GWV
 - > Highest priority for GWV research
 - > Complex challenges
 - > Requires committed, comprehensive effort