

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 (IQM, 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, IQM, 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

NATIONAL 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 (conditions) 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).
- Encourage patients to take an active role in their recovery.

The content of this guideline reflects the current state of knowledge and is subject to change as new evidence emerges. The content of this guideline is not intended to be used as a substitute for clinical judgment. The National Clinical Practice Guideline for the Management of Medically Unexplained Symptoms (MUS), Chronic Pain and Fatigue is available at: www.va.gov/opa/whedoc/whedoc030504.htm

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Clinical Practice Guidelines: Medically Unexplained Fatigue and Pain

THERAPY INTERVENTIONS FOR FIBROMYALGIA

Intervention	Study Design	Relative Benefit	Priority Ranking
A	Cognitive Behavioral Therapy (CBT) Graded Aerobic Exercise Antidepressant (TCA)	Antidepressant Cognitive behavioral therapy Graded aerobic exercise	High
B	CBT Graded aerobic exercise Antidepressant (SSRI/SNRI/SSRI)	Antidepressant Cognitive behavioral therapy Graded aerobic exercise	Medium
C	Graded aerobic exercise Antidepressant (SSRI/SNRI, anti-TCA)	Graded aerobic exercise Antidepressant	Low
D	Antidepressant (SSRI/SNRI)	Antidepressant	Very Low

†Relative ranking is based on the magnitude of the effect size (ES) for each intervention. ‡Relative ranking is based on the magnitude of the effect size (ES) for each intervention. ††Relative ranking is based on the magnitude of the effect size (ES) for each intervention.

THERAPY INTERVENTIONS FOR CFS

Intervention	Study Design	Relative Benefit	Priority Ranking
A	Cognitive Behavioral Therapy (CBT) Graded Aerobic Exercise	Cognitive behavioral therapy Graded aerobic exercise	High
B	CBT Graded aerobic exercise Antidepressant (SSRI/SNRI)	Cognitive behavioral therapy Graded aerobic exercise Antidepressant	Medium
C	Graded aerobic exercise Antidepressant (SSRI/SNRI)	Graded aerobic exercise Antidepressant	Low
D	Antidepressant (SSRI/SNRI)	Antidepressant	Very Low

†Relative ranking is based on the magnitude of the effect size (ES) for each intervention. ‡Relative ranking is based on the magnitude of the effect size (ES) for each intervention. ††Relative ranking is based on the magnitude of the effect size (ES) for each intervention.

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Clinical Practice Guidelines: Medically Unexplained Fatigue and Pain

PHARMACOLOGIC AGENTS FOR CFS/FM*

Agent	Dose Studied	Effects	Adverse Effects	Comments
Antidepressants	150-300 mg/day 300-600 mg/day	Yes	Headache, weight gain, constipation, dry mouth, dizziness, blurred vision	The agent is effective in approximately 50% of patients. The response rate is not well understood. Antidepressants are not recommended for CFS/FM.
Antipsychotics	15-40 mg/day	Yes	Weight gain, constipation, dry mouth, blurred vision	The agent is effective in approximately 50% of patients. The response rate is not well understood. Antipsychotics are not recommended for CFS/FM.
Anticholinergics	1-2 mg/day 4-16 mg/day 16-32 mg/day	Yes	Blurred vision, dry mouth, constipation, weight gain	The agent is effective in approximately 50% of patients. The response rate is not well understood. Anticholinergics are not recommended for CFS/FM.
Antihistamines	10-20 mg/day 10-20 mg/day 10-20 mg/day	Yes	Sedation, drowsiness, dry mouth, constipation, weight gain	The agent is effective in approximately 50% of patients. The response rate is not well understood. Antihistamines are not recommended for CFS/FM.
Anticonvulsants	100-200 mg/day 100-200 mg/day 100-200 mg/day	Yes	Dizziness, weight gain, constipation, dry mouth, blurred vision	The agent is effective in approximately 50% of patients. The response rate is not well understood. Anticonvulsants are not recommended for CFS/FM.
Antiemetics	10-20 mg/day 10-20 mg/day 10-20 mg/day	Yes	Sedation, drowsiness, dry mouth, constipation, weight gain	The agent is effective in approximately 50% of patients. The response rate is not well understood. Antiemetics are not recommended for CFS/FM.
Antiparkinsonian agents	10-20 mg/day 10-20 mg/day 10-20 mg/day	Yes	Dizziness, weight gain, constipation, dry mouth, blurred vision	The agent is effective in approximately 50% of patients. The response rate is not well understood. Antiparkinsonian agents are not recommended for CFS/FM.
Antibiotics	10-20 mg/day 10-20 mg/day 10-20 mg/day	Yes	Dizziness, weight gain, constipation, dry mouth, blurred vision	The agent is effective in approximately 50% of patients. The response rate is not well understood. Antibiotics are not recommended for CFS/FM.
Antifungal agents	10-20 mg/day 10-20 mg/day 10-20 mg/day	Yes	Dizziness, weight gain, constipation, dry mouth, blurred vision	The agent is effective in approximately 50% of patients. The response rate is not well understood. Antifungal agents are not recommended for CFS/FM.
Antiviral agents	10-20 mg/day 10-20 mg/day 10-20 mg/day	Yes	Dizziness, weight gain, constipation, dry mouth, blurred vision	The agent is effective in approximately 50% of patients. The response rate is not well understood. Antiviral agents are not recommended for CFS/FM.
Antiparasitic agents	10-20 mg/day 10-20 mg/day 10-20 mg/day	Yes	Dizziness, weight gain, constipation, dry mouth, blurred vision	The agent is effective in approximately 50% of patients. The response rate is not well understood. Antiparasitic agents are not recommended for CFS/FM.

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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

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GWVI 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 %

GWVI 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 GWI?

Identification of Treatments for GWI: Approaches Used by VA

Levels of Evidence (IQM, 2001)

- Level
- 1 Multiple well-designed RCTs; multiple well-designed outcomes studies
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GWVI Treatment Research: What Next?

- Identifying/evaluating additional GWI treatments
 - > Identification of specific biological mechanisms underlying GWI
 - 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

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