

Appendix

Presentation 1 – Lea Steele

CFS, Fibromyalgia, and MCS:

**Defined "Chronic Multisymptom Illnesses"
in Relation to Gulf War Veterans' Illnesses**

Lea Steele, Ph.D.

Meeting of the Research Advisory Committee
on Gulf War Veterans' Illnesses
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"Chronic Multisymptom Illnesses" in the General Population

- Unexplained symptom complexes: Historical context
- Overlap: Are they all the same?
- Multisymptom illnesses found in civilians in relation to Gulf War veterans' illnesses

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"Chronic Multisymptom Illnesses": Historical Context

- 1750: *Febricula* (Manningham) great lassitude and weariness, "flying pains", memory problems, most common in women
- 1869: *Neurasthenia* (Beard) persistent fatigue, headaches, difficulty concentrating, memory loss, diffuse pain, sleep disturbances
- 1871: *Irritable heart* or soldiers' disease (Da Costa) in Civil War veterans: fatigue, dizziness, headache, breathlessness, sleep disturbances

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"Chronic Multisymptom Illnesses": Historical Context

**Epidemic Fatigue Syndromes (Over 60 in the medical literature):
extreme fatigue, headache, weakness, somatic pain, cognitive
difficulties, neuro symptoms**

- > 1934: Los Angeles, CA
- > 1948: Akureyri, Iceland *"Icelandic Disease"*
- > 1949: Adelaide, Australia
- > 1954: Tallahassee, FL, Seward, AK *"Epidemic Neuromyasthenia"*
- > 1956: Punta Gorda, Florida
- > 1984: Incline Village, NV *"Chronic Fatigue Syndrome"*
- > 1985: Lyndonville, NY

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Contemporary "Chronic Multisymptom Illnesses (CMI)"

- **Chronic Fatigue Syndrome (CFS, CFIDS)**
 - > Myalgic encephalomyelitis (ME)
 - > Post-viral fatigue syndrome
- **Fibromyalgia (fibromyalgia syndrome, FMS, fibrositis)**
- **Multiple Chemical Sensitivity (MCS)**
 - > Environmental illness
 - > Sick building syndrome
- **Others: "Chronic Lyme Disease", IBS, MPS, TMD etc**

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"Chronic Multisymptom Illnesses"

Multiple symptoms affecting multiple organ systems:

- Symptoms not adequately explained by other diagnoses
- Etiology, underlying pathophysiology not clear
- Rarely associated with objective diagnostic indicators

Substantial overlap between symptoms of these conditions

- Fatigue, sleep difficulties
- Cognitive problems, mood disturbances
- Somatic pain
- Other (persistent headaches, GI problems, etc)

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Contemporary "Chronic Multisymptom Illnesses (CMI)":
Are They All the Same Thing?

A Venn diagram with three overlapping circles. The top circle is labeled "Chronic Fatigue Syndrome". The bottom-left circle is labeled "Fibromyalgia". The bottom-right circle is labeled "Multiple Chemical Sensitivity". The circles overlap in the center and in pairs.

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Multisymptom Syndromes Defined Differently

- CFS "gateway" defining symptom is significant, persistent fatigue
- FMS "gateway" defining symptom is pain
- MCS syndrome defined by patient's adverse response to chemicals

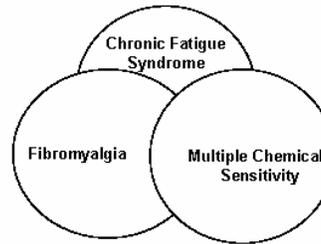
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Overlap Between CFS, FMS, and MCS

Symptoms of fatigue, somatic pain, and sensitivity to chemicals are common in patients with all 3 syndromes, but degree of overlap of defined syndromes varies in different studies and populations.

- *Buchwald (1994)*: 70% of FMS patients and 30% of MCS patients meet criteria for CFS
- *White (2000)*: 58% of FMS patients meet criteria for CFS
- *Jason (2000)*: 40% of CFS patients meet criteria for MCS, 16% meet criteria for FMS
- *Aaron (2000)*: CFS patients: 80% dx with FMS, 4% dx with MCS
FMS patients: 18% dx with CFS, 18% dx with MCS

"Chronic Multisymptom Illnesses" Overlap: Specific Diagnosis Depends on A Variety of Factors



Why Study "Civilian" Chronic Multisymptom Illnesses (CMI) in Relation to Gulf War Veterans' Illnesses?

- **Clinical similarities**
 - Many of the same symptoms in GWI, CMI patients
 - Objective diagnostic tests not generally useful
- **Possible biological similarities**
 - Similar etiologic factors? (exposures? genetic factors? infection? psych factors?)
 - Similar underlying pathophysiological processes?

Why Study "Civilian" Chronic Multisymptom Illnesses (CMI) in Relation to Gulf War Veterans' Illnesses?

- **Social and historical context similar**
 - CMIs often unrecognized/dismissed by clinicians, considered primarily psychiatric; challenging for both patients and healthcare providers
 - Controversial/political aspects: patient advocacy groups historically at odds with federal agencies charged with research
- **Progress in study of CMI may be applicable to GWI**
 - Similar methods required for study of symptom complexes without clinical markers
 - Clues from what is known re: neurological, immune, endocrine abnormalities in civilian CMI
 - CMI treatments may benefit veterans with GWI

Why Study "Civilian" Chronic Multisymptom Illnesses (CMI) in Relation to Gulf War Veterans' Illnesses?

- ★ Studies consistently find prevalence of CFS and other CMIs to be higher in Gulf War veterans than in nondeployed, era veterans

Prevalence of CFS in Gulf War Veterans

Study	Population	CFS cases	Prevalence of CFS
Bourdette, 2001	357 Gulf War vets in WAOR	Clinically diagnosed CFS	2.2 % PGW (min)
Fukuda, 1998	158 Air Guard Gulf War vets	Clinically diagnosed CFS	5.1 % PGW
Canadian MOD, 1998	6,552 Gulf and era vets	Symptom-based CFS estimate	8.5 % PGW, 1.9 % era; OR = 5.3*
Gray, 2002	6,935 Navy Seabees	Self-report of physician dx	5.2 % PGW, 0.7% era; OR = 7.6*
Kang, 2003	20,917 Gulf and era veterans	Symptom-based CFS estimate	5.6 % PGW, 1.2 % era; OR = 4.8*
Steele, 2000	2,030 Kansas Gulf, era vets	Symptom-based estimate	7.1 % PGW, 0.7 % era; OR = 8.2*
Unwin, 1999	5,157 U.K. Gulf, era veterans	Self-report of physician dx	3.3% PGW, 0.3 % era; OR = 4.4*
Australian study, 2003	3,044 Australian Gulf, era vets	Self-report of phys dx/strtd	1 % PGW, 1 % era; OR = 0.8

*statistically significant, p<.05

Prevalence of Fibromyalgia in Gulf War Veterans

Study	Population	FMS cases	Prevalence of Fibromyalgia
Bourdette, 2001	357 Gulf War vets in WAOR	Clinically diagnosed FMS	2.5 % PGW (min)
Canadian MOD, 1998	6,552 Gulf and era vets	Symptom-based FMS estimate	16.2 % PGW, 9.6 % era; OR = 1.8*
Iowa study	3,655 Iowa Gulf and era veterans	Symptom-based FMS estimate	18.2% PGW, 9.2% era; prev dif: 7.7*
Steele, 2000	2,030 Kansas Gulf, era vets	Self-report of physician dx	2.0% PGW, <0.5 % era; OR = 3.7
Smith, 2000	Gulf, era vets in military hosp	Hospitalized for FMS	0.04 % PGW, 0.04 % era; OR = 1.2*

*statistically significant, p<.05

Prevalence of MCS in Gulf War Veterans

Study	Population	MCS cases	Prevalence of MCS
Black, 2000	3,695 Iowa Gulf and era vets	Study-defined	5.4 % PGW, 2.6 % era; OR = 1.92*
Canadian MOD, 1998	6,552 Gulf and era vets	Resp to chems w/ 2+ symp types	2.7 % PGW, 0.9 % era; OR = 4.01*
Gray, 2002	6,935 Navy Seabees	Self-report of physician dx	1.6 % PGW, 0.4% era; OR = 4.5*
Proctor, 2001	226 Mass. Gulf and era vets	Cullen def, based on symps	2.9% PGW, 0% era
Reid, 2001	5,965 UK Gulf and era vets	Simon def, based on symps	1.3 % PGW, 0.2 % era; OR = 6.9*
Unwin, 1999	5,157 U.K. Gulf and era vets	Self-report of physician dx	0.8 % PGW, 0.3 % era; OR = 2.2
Australian study, 2003	3,044 Australian Gulf, era vets	Self-report of phys dx/strtd	<1 % PGW, <1 % era; OR = 1.3

*statistically significant, p<.05

Summary:
 Prevalence of CMI in Gulf Veterans Compared to Era Veterans

CFS: 2.2 - 8.5 % of US, UK, Canadian Gulf veterans
 ORs significantly elevated: ORs = 4.4 - 8.2

FMS: Few prevalence estimates, highly variable
 2% dx FMS, ~16% based on symptom estimates; ORs = 1.2 - 3.7

MCS: Variable estimates based on MCS definition
 Physician-diagnosed MCS low (< 2 %),
 Defined MCS higher (1.3 - 5.4%); ORs = 1.1 - 6.9

***Symptoms of chronic fatigue, widespread pain, and chemical sensitivity reported by higher proportion of Gulf War veterans*

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Symptom of Chemical Sensitivity vs. MCS in Gulf Veterans

<i>Study</i>	<i>% of Gulf vets reporting symptom</i>	<i>"MCS" in Gulf Vets</i>
Black (2000)	13%	5%
Canadian (1998)		3%
Gray (2002)		2%
Fukuda (1998)	5%	
Kang (2000)	15%	
Proctor (2001)		3%
Reid (2002)	28%	1%
Steele (2000)	17%	

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Distinctions between "Civilian" CMIs and Gulf War Illnesses

- **Occurrence of CMI and GWI**
 - > CFS appears to be 10-20 times more common in Gulf vets than the general population
 - > FMS and MCS rates in comparison to general population not clear
 - > Association of CMI with age, female sex less prominent in Gulf vets than in civilian populations
 - > CFS, FMS, MCS case criteria do not adequately describe the majority of veterans affected by excess chronic symptom complexes

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Use of CFS Case Definition in Describing GWI "Cases"

- In 1994, the Defense Science Board recommended that research on illnesses affecting Gulf War veterans be coordinated with federal CFS research efforts
- A GWI case definition modeled after the CFS case definition was proposed by the federal Persian Gulf Veterans Coordinating Board
- Lacking an accepted GWI case definition, some investigators have used the CFS case definition to distinguish ill "cases" from "controls" among symptomatic Gulf War veterans
 - > Does CFS case def describe a meaningful subgroup of ill Gulf veterans?
 - > Are Gulf War veteran CFS cases similar to CFS cases in the general population?

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Comparing Symptoms of Gulf Veterans with CFS to People in the General Population

Comparisons between CFS-related symptoms reported by Gulf veterans and a population-based sample in San Francisco (Steele) indicate:

- The CFS case definition identifies a highly symptomatic subgroup of Gulf War veterans, but accounts for only a fraction of the excess symptomatology observed in Gulf War veterans.
- Gulf War veterans who meet the CFS case definition also appear to differ symptomatically and demographically from CFS patients in the general population

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Persistent Symptoms of Gulf Veterans Who Meet CFS Criteria vs. Symptoms Associated with CFS in a Population Sample

More Prevalent (by >15%) in Gulf War Veterans
Joint pain
Headache
Numbness, tingling in extremities
Night sweats
Diarrhea
Skin rashes

Less Prevalent (by >15%) in Gulf War Veterans
Sleep disturbances
Depression
Unwell after exertion
Sorethroat

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Distinctions between "Civilian" CMI's and Gulf War Illnesses: Research Considerations

- "Civilian" CMI Research
 - > Research is challenging: no clear "case" group or "at risk" group to study
 - > Research guidelines and widely used case definitions have helped to standardize research in CFS, FMS
 - > Scientific progress: Thousands of studies done, providing detailed information re: epidemiological, neurological, endocrine, immunological, and psychiatric aspects of CMI conditions
- GWV Research
 - > Research, in theory, should be less challenging: defined cohort was healthy at one point in time, shared common experiences before becoming ill; nondeployed era veterans provide suitable "unexposed" comparison group
 - > Less progress in describing key physiological and epidemiological parameters of the conditions
 - > Research methods, case definitions not yet standardized

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Gulf War Illnesses in Relation to "Civilian" CMI: The Bottom Line

- Many similarities between GWV and multisymptom conditions found in the general population
- CFS, possibly other defined CMI syndromes, are more common in U.S. Gulf veterans than the general population
- Much to be learned from research on CMIs that may contribute to understanding and treating GWV
- Not clear whether CFS, FMS, or other defined CMIs represent distinct clinical entities or symptom complexes resulting from multiple overlapping causes and pathophysiological processes.

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"Is it a Unique Disease Entity?"
Question Asked re: All Multisymptom Illnesses

A Venn diagram consisting of three overlapping circles. The top-left circle is labeled "Chronic Fatigue Syndrome". The top-right circle is also labeled "Chronic Fatigue Syndrome". The bottom circle is also labeled "Chronic Fatigue Syndrome".

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"Is it a Unique Disease Entity?"
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GWI likely fits into the CMI "Overlapping Syndrome" Diagram but precisely how and where it fits is unclear

A Venn diagram with four overlapping circles. The top-left circle is "Chronic Fatigue Syndrome", the bottom-left is "Fibromyalgia", and the bottom-right is "Multiple Chemical Sensitivity". A fourth circle, "Gulf War Illnesses", is positioned to the right. An arrow points from this circle to the intersection of "Chronic Fatigue Syndrome" and "Multiple Chemical Sensitivity", with a question mark above the arrow.

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Speakers

Multiple Chemical Sensitivity	Dr. Bill Meggs Dr. Iris Bell
Chronic Fatigue Syndrome	Dr. Bill Reeves
Fibromyalgia, treating CMI	Dr. Dan Clauw

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