Presentation 3 – Roberta White

Effects of Pyridostigmine Bromide and PTSD on Neuropsychological Function in GW Veterans

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Introduction - 1

Gulf War illness symptoms generally include memory and concentration difficulties, fatigue, headache and joint pains.

Introduction - 2

Suggested causes of Gulf War illness include exposure to environmental toxicants (diesel fuels, pesticides, pyridostigmine bromide use, biological or chemical warfare agents) and acute stress reactions.

Introduction - 3

Due to limited record keeping by the military and GW veterans' lack of awareness concerning potential environmental contaminants, it has been virtually impossible to definitely assess exposures in the veteran group.

Introduction - 4

However, it seems likely that GW veterans would recall with some accuracy whether they used the anti-nerve gas agent pyridostigmine bromide (PB) due to the fact that the pills were self-administered.

Pyridostigmine Bromide -1

PB is an acetylcholine (ACh) inhibitor used in the GW to protect US veterans against chemical weapon attacks.

PB - 2

PB reversibly binds to ACh receptors in the peripheral nervous system, providing protection from chemical weapon exposures (soman, sarin) that irreversibly bind to ACh receptors.

PB - 3

PB generally does not cross the blood brain barrier or have centrally acting effects. However, evidence from animal models suggests that PB taken during periods of stress may affect the central nervous system (CNS). In humans, this might result in confusion, fatigue and cognitive difficulties.

Post-Traumatic Stress Disorder (PTSD)

Stress has been suspected as a cause of GW illness.

PTSD - 2

Severe stress reactions result in the diagnosis of PTSD. A chronic state of arousal may occur when individuals with PTSD are exposed to triggers similar to the original traumatic event.

PTSD - 3

Exposure to traumatic or stressful events has been associated with cognitive impairments such as diminished attention on tracking tests.

PTSD - 4

PTSD has been associated with memory and attention deficits in US Gulf War veterans.

Study Aims

- Assess the impact of PB use and PTSD diagnosis on cognitive functioning in GW veterans.
- Assess the separate impact of each exposure on cognition and then the combined effect of PTSD and PB use.

Participants - 1

Treatment seeking veterans from the VA Boston Healthcare System who were in the military during the time of the Gulf War (1990-1991) were eligible for study participation.

Participants - 2
GW-deployed veterans

1. Randomly selected GW veterans seeking treatment or diagnostic evaluation for any health complaint.
2. GW veterans clinically referred for a neuropsychological evaluation due to increased cognitive or health symptom complaints.

Participants - 3

A control group of VABHS treatment seeking GW-era veterans who were not deployed to the Gulf were randomly recruited and evaluated.

Participants - 4

A total of 207 GW-deployed participants were recruited for the study.

53 GW-era veterans participated.

Participants - 5
GW-deployed group

92 GW-deployed veterans reported using PB during the GW.

28 GW-deployed veterans met criteria for PTSD based on CAPS-DX criteria.

Participants - 6

Mean age and sex were different among GW-deployed and non-GW-deployed participants.

Mean age and sex were not significantly different between participants with and without PB use or those with and without PTSD diagnoses.

Methods - 1

All study participants underwent a semi-structured clinical interview, the Clinician Administered PTSD scale (CAPS-DX), and a neuropsychological test battery.

Methods - 2

PTSD diagnosis was made by the CAPS-DX, an instrument specifically designed for PTSD diagnosis.

Methods - 3

PB exposure was determined by a self-report questionnaire inquiring about environmental exposures while in the Gulf War.

Neuropsychological Test Battery - 1: General Intellectual Function

Wechsler Adult Intelligence Scale-Revised (WAIS-R), Information subtest

Neuropsychological Test Battery - 2: Attention and Executive Function

- Continuous Performance Test (CPT)—computerized
- WAIS-R Digit Spans
- Wechsler Memory Scale- Revised (WMS-R), Digit Spans
- Trail-making Test
- Stroop Test
- Paced Auditory Serial Arithmetic Test
- Wisconsin Card Sorting Test

Neuropsychological Test Battery - 3: Motor Function

- Finger Tapping Test
- Purdue Pegboard Test

Neuropsychological Test Battery - 4: Visuospatial Abilities

- WAIS-R Block Designs
- Hooper Visual Organization Test

Neuropsychological Test Battery - 5: Memory

- WMS-R Verbal Paired Associate Learning
- California Verbal Learning Test
- WMS Visual Reproductions, immediate and delayed recall
- Rey-Osterreith Complex Figure, immediate and delayed recall

Neuropsychological Test Battery - 6: Motivation

- Test of Memory Malingering
- Internal consistency measures

Neuropsychological Test Battery -7: Mood

- Profile of Mood States

Statistical Analyses -1

The significance of the findings were evaluated in a two-step process:

- Multivariate analyses of covariance were performed for each neuropsychological domain.
- Univariate analyses were performed for each specific test.

Statistical Analyses - 2

- Analyses for GW-deployed veterans (N=207) and non-deployed veterans (N=53) controlled for age and sex
- Effects of self-reported PB exposure (N=92) and PTSD diagnosis (N=28) were analyzed within the group of 207 GW-deployed veterans

Results: Deployed vs. non-deployed veterans

- Deployed veterans performed worse on measures assessing
  - Attention
  - Motor and visuomotor skills
  - Visual memory
  - Mood and motivation

Results - Domain Specific Analyses GW-deployed group

	PB P value	PTSD P value	PB x PTSD P value
Attention	.14	.53	.52
Executive Functions	.01*	.92	.91
Motor / Visuomotor	.89	.72	.82
Verbal Memory	.12	.19	.29
Visual Memory	.38	.53	.53
Mood and Memory	.09	.05*	.17

Results - Mood Scales GW-deployed group

MOOD	PB PTSD	Exposure No PTSD	No PB PTSD	Exposure No PTSD	PB P value	PTSD P value	PB x PTSD P value
POMS Tension (t)	51.8	42.5	58.3	43.3	.10	.004	.44
POMS Depression (t)	49.2	42.6	55.3	44.3	.38	.04	.61
POMS Anger (t)	53.5	47.7	57.8	49.3	.45	.15	.72
POMS Vigor (t)	30.1	32.3	47.3	34.8	.91	.37	.93
POMS Fatigue (t)	57.7	51.9	60.5	53.3	.03	.30	.61
POMS Confusion (t)	54.9	44.2	53.0	48.3	.20	.75	.20

Results - Executive Tasks GW-deployed group

	PB PTSD	Exposure No PTSD	No PB PTSD	Exposure No PTSD	PB P value	PTSD P value	PB x PTSD P value
WCST #Sorts	3.5	3.5	4.8	3.9	.01	.49	.40
Stroop ĞWords	84.7	92.0	76.0	90.5	.68	.84	.75
Stroop ĞColrs	65.3	65.9	64.5	71.7	.19	.88	.98
Stroop ĞWord/Color	41.0	39.2	37.5	39.1	.43	.84	.73
PASAT-trials 1-4	124.1	121.2	107.0	123.3	.32	.76	.60
Trail Making B (time)	77.6	73.9	72.8	67.2	.34	.50	.55

Conclusions -1

PTSD diagnosis was significantly associated with the mood indices of POMS test (tension and depression). However, it was not significantly associated with cognitive functioning in this cohort.

Conclusions - 2

Self-reported PB use was significantly associated with executive system functioning in this cohort of GW veterans.

Conclusions - 3

There were no interaction effects of PB use and a diagnosis of self-reported PTSD in the group of veterans.

Follow-up study: Preliminary results (6/12/03)--1

- Paired t-tests show no changes in performance on most neuropsychological tests among GW-deployed veterans
- Exceptions (worse performance):
  - Digit Spans backward
  - Wisconsin Card Sorting Test
  - Purdue Pegboard

Follow-up study: Preliminary results (6/12/03) - 2

GW veterans report more symptoms than they did 3 years previously:

Symptom	Time 1	Time 2
Headaches	62%	80%
Fatigue	59%	88%
Forgetfulness	63%	81%
Joint pain	46%	88%
Skin rash	32%	61%

Follow-up study: Preliminary results (6/12/03) - 3

- Diagnosis of PTSD is associated with increased mood complaints but not diminished cognitive function
- Self-reported PB exposure is associated with lower scores on tests assessing visuomotor function (Trails B, Finger Tapping non-dominant hand, Block Designs) and possibly memory (CVLT-short delay)

History of Work

- Ft. Devens survey—1991 (N = 3000)
- Clinical study (VA)—1993-1994
- BEHC studies (VA)—1994-2000
- DoD study 1—1996-1999
- CDC studies—1997-2001
- DoD study 2—2000-2003

Ft. Devens results - 1 (June 3, 1994 - 2000)

- Self-reported PB exposure was *not* predictive of these classes of symptoms:
  - Gastrointestinal
  - Musculoskeletal
  - Neurological
  - Neuropsychological
  - Psychological

Ft. Devens result - 2

Self-reported PB exposure was *not* related to neuropsychological test performance

DISCUSSION

- Treatment-seekers vs. non-treatment seekers
- Vulnerability/risk factors
- Future directions