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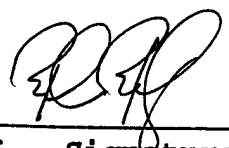

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DoD Annual Report
October 1998

Illness Among Persian Gulf War Veterans: Case Validation Studies, Grant # DAMD17-97-1

Introduction

We recently completed a population-based, cross-sectional telephone survey of 4,886 military personnel to compare the prevalence of self-reported symptoms and illnesses among military personnel either deployed, or eligible but not deployed, during the Persian Gulf War (PGW) (JAMA, 1997) funded by the Centers for Disease Control and Prevention. Compared with non-PGW military personnel, PGW military personnel reported a significantly higher prevalence of symptoms of a variety of conditions, although depression, cognitive dysfunction, and fibromyalgia were particularly elevated. The existence of a causal relationship between either military exposures or other risk factors and documented illness for most symptomatic PGW veterans remains to be demonstrated.

This study, a series of case-validation and case-control studies nested within the previous population-based cohort study, should provide an estimate of the true magnitude of the problem. Because of the magnitude of the difference in prevalence between these groups, it is critical to explore and characterize the degree to which the groups exhibit cognitive deficits, depression, and fibromyalgia. The primary purpose of the current project is to compare the true rate of confirmed disease among samples of veterans deployed to the Gulf with and without these predefined conditions, versus true rate of confirmed disease among samples of veterans not deployed, with and without these self-reported conditions. Furthermore, we also plan to attempt to identify risk factors for each validated illness outcome of interest including medical and family history, psychological factors (such as major lifetime events or stress, personality traits, and social support), and occupational and environmental exposures in a series of nested case-control studies.

Over the past year substantial progress has been made in laying the foundation for the project and getting the project underway. Staffing and instrument selection are nearly complete, and pilot testing is planned over the next 3 weeks. We plan to begin assessing research subjects in mid-November 1998. Using a conservative estimate of 1.3 subjects assessed per day on average, we will have completed assessments of all 900 study subjects by early August, 2001. We have developed several contingency plans in order to finish subject recruitment and evaluation on or before the date specified in the original proposal.

Personnel

The new research personnel positions required for the grant have either been filled or are about to be filled. The Study Coordinator position was filled in June 1998, and the Senior Programmer Analyst position was filled in September 1998. Both positions were considered crucial to fill before the remaining personnel could be hired. Importantly, both position descriptions were developed, reviewed and submitted to our human resources office by early December, 1998. Due to increasing competition in the area for experienced programmers, hiring of the programmer/analyst was particularly challenging and time-consuming. However, we are very pleased with the background and expertise of the individuals we were able to recruit for both positions.

Two physicians have been interviewed and selected to perform the planned history and physical examinations on a part-time basis. They have each undergone additional training in the detailed neurologic and musculoskeletal examinations by specialists in these clinical areas in the past 3 months specifically for the purposes of this study.

The recruitments of a full-time Research Assistant II and the part-time neuropsychology Research Assistant II positions are in the final stages, having been listed, advertised, and an initial round of interviews completed. We are in the process of checking references and scheduling a final round of interviews on the finalists, with a projected hire date of early November 1998 for both positions.

Dr. Mark Ross, the neurologist slated to serve as a co-investigator on the project, left UIHC in the late summer of 1998 to accept a position at the University of Kentucky. Dr. Gwendolyn Ford, a neuromuscular disorder specialist and a recent addition to UIHC's Department of Neurology, has been selected to replace Dr. Ross as a co-investigator. Dr. Ford came to UIHC from the US Army, and has considerable expertise in evaluating Persian Gulf war veterans, a background that should be particularly advantageous for this project.

Appendix A depicts the personnel associated with the project.

Research Methods

Throughout the past year we have been holding bi-monthly meetings in which all personnel involved in the project have the opportunity to discuss theoretical issues, methodological issues, and any other topic related to the study. This forum has proven invaluable for refining the research questions and for addressing practical questions regarding research procedures and methodology. We also hold regular and ad hoc meetings of key personnel to address specific considerations, such as instrument development, sampling issues, data security and database development issues, and other issues in order to implement the project successfully.

The overall study design is essentially unchanged from the grant proposal. However, there have been some specific refinements to the specifics of the evaluation, study sample selection and procedures that the investigators have discussed and agreed will improve the study. One item that has been modified is the portion of the study that will look at multisystemic conditions – this will now focus specifically on the condition of fibromyalgia. The planned assessment for these subjects has not changed significantly, however, we have chosen this more homogeneous group of subjects in order to attempt to draw more solid conclusions from the planned studies. Importantly, we have decided it is preferable to focus on subjects reporting symptoms consistent with the diagnosis of fibromyalgia, since the difference between exposed and unexposed subjects was so great with regard to this condition. Additionally, this subset of the three multisystemic conditions typically are the only group that has a physical examination finding that may be reproduced, e..g., tender points. Finally, further analyses have demonstrated considerable overlap between this and the other multisystemic conditions.

We have also made some modifications to the list of instruments to be used in the psychiatric and psychological examination. Several of the investigators with expertise in this area were concerned about some of the instruments that heavily relied on self-report of symptoms. To maximize the breadth of the assessment, minimize redundancies, and use several different approaches to assess certain traits as a validity tool, we have eliminated seven instruments that appeared in the original grant proposal and we have added three new instruments. Specifically, we have eliminated the Clinician Administered Post-Traumatic Stress Scale (CAPS), the Structured Clinical Interview for DSM-IV Personality Disorders (SIDP-IV), the Family History Research Diagnostic Criteria (FH-RDC), the Beck Depression Inventory (BDI), the Brief Symptom Inventory (BSI), the Life Experience Survey (LES), and the Neo Five Factor Inventory (Neo-FFI). We have added the Schedule of Nonadaptive and Adaptive Personality (SNAP), the Mood and Anxiety Symptom Questionnaire (MASQ), and the Brief Life Stress Questionnaire (BLSQ). The SNAP is a standard instrument designed to assess personality constructs and styles, which replaces the SIDP-IV and Neo-FFI. Additionally, it provides validity scales, which were considered to be particuarly important in this setting. The BLSQ is an instrument developed by the investigators, based on the LES and other life stress instruments, but specifically adapted to this clinical setting. Specific questions on family history, based on those in the FH-RDC, have been developed for the purposes of this study, in order to minimize subject burden and collect the most important information. Additionally, we have decided to expand the use of the MMPI to all subjects, not just those in studies 1 and 2. The MMPI also provides another assessment of personality, but has an embedded validity scale which will be useful in conjunction with the concurrent use of the SNAP.

We have also been reviewing a series of instruments to assess general health status. The two final candidates to fill this role are the Health Utilities Index (HUI) and the Quality of Well Being scale (QWB). It is important to note that these

decisions have involved extensive discussions between the study investigators, review of the current literature, and consultation with outside experts in each area. Appendix B presents all the data collection instruments we plan to use in the project.

In addition to the primary data that will be generated in this project, we will utilize secondary data to assess pre-deployment health status variables, as well as post-deployment data associated with our research subjects. We have been working with the Defense Manpower Data Center (DMDC) to secure access to data relevant to this project. These data will include variables collected at enlistment and throughout an individual's military tenure. This information will help in the assessment of pre-existing states/conditions, help in controlling for pre-deployment health status and will also potentially serve as a validity check for a variety of self-reported variables.

In preparation for the collection of the study's primary data we are preparing a series of databases for the purpose of data entry and data management. These databases bear a close visual resemblance to the instruments that will be used for collecting and coding the data, will have built in quality-control features (such as accepting only values or scores that fall within the valid range), and will conform to rigid security standards.

We have a request submitted to utilize the facilities of the UIHC's General Clinical Research Center. Use of these facilities will streamline the assessment of subjects and provide an optimal clinical research setting for the project. Instead of transporting subjects to different parts of the hospital to undergo the various facets of the assessment, subjects will be located centrally in the GCRC that is designed for patient assessment. The research assessments and personnel will revolve around this location. An additional benefit of utilizing the GCRC facilities is the availability of phlebotomy services performed by experienced GCRC staff.

Research Subjects

As outlined in the grant proposal we plan to assess 900 of the 3,695 subjects who participated in the telephone survey that assessed self-reported illness among Persian Gulf War veterans. The sample for the current study will be limited to subjects whose residence is in Iowa or a bordering state (Illinois, Minnesota, Missouri, Nebraska, South Dakota, or Wisconsin). Based on subjects' residing address at the time of the telephone survey, this geographic heuristic yields a pool of 2,464 subjects from which to draw (1,289 exposed, 1,175 not exposed). Tables 1 through 3 break this pool out by the three conditions of interest in this project (cognitive dysfunction, depression, and fibromyalgia) and exposed/not exposed status. Based on these analyses, we

have further revised our sampling strategy, based primarily discussions between Drs. Doebbeling and Woolson, as well as review by the study investigators.

Table 1: Potential Subjects for Cognitive Dysfunction Study

	Symptomatic	Not Symptomatic	Total
Exposed	290	999	1289
Not Exposed	99	1076	1175
Total	389	2075	2464

Table 2: Potential Subjects for Depression Study

	Symptomatic	Not Symptomatic	Total
Exposed	225	1064	1289
Not Exposed	131	1044	1175
Total	356	2108	2464

Table 3: Potential Subjects for Fibromyalgia Study

	Symptomatic	Not Symptomatic	Missing	Total
Exposed	300	989		1289
Not Exposed	144	1030	1	1175
Total	444	2019		2464

Pilot Testing

We have made arrangements to assess approximately ten to twenty pilot subjects prior to the assessment of the study's research subjects. This will yield a first-hand estimate of the time needed for the assessments, and it will allow any last-minute modifications to the research procedures before proceeding with research subjects.

Pilot subjects will be volunteers drawn from the Army National Guard unit based in Iowa City, Iowa. Any members of this unit who participated in the original telephone survey will be excluded from the pilot phase of the study.

Schedule

Pilot testing is planned for mid-November and will require approximately one to two weeks. Once the pilot testing is thoroughly debriefed, and the assessments revised as necessary, we will be ready to begin assessing research subjects. This process will probably begin in early-December, 1998. Assuming a conservative average of 1.3 subjects assessed per day, the subject assessment phase of the study should end by early August, 2001 at the latest.

Conclusion

This project is on track to begin assessing Gulf War veterans before year's end. Most key positions have been filled, and the two positions that remain to be filled are in the final stage of the recruitment process. We have put a great deal of effort into further refining and developing our research procedures, and we are close to finalizing our list of research instruments. Pilot testing will take place soon, and the information that process yields should help ensure a smooth transition to the assessment of our research subjects.

Appendix A. Study Personnel

Principal Investigator:	Bradley Doebbeling, MD, MSc
Co-Investigators:	Joseph Barrash, PhD Donald Black, MD Gwendolyn Ford, MD Kenneth Saag, MD David Schwartz, MD Robert Woolson, PhD Thoru Yamada, MD
Study Coordinator:	John Holman, MA
Senior Programmer Analyst:	Mary Howard, MA, MS
Clinicians	Dina Jantzen, MD Robert Zwicki, DO
Research Assistant:	TBD October 1998
Research Assistant (Neurology):	TBD October 1998

Note: Several additional investigators have been regular participants in the study group, making regular contributions to the study and participating out of personal or scientific interest. These include two of our consultants and multiple other investigators: Drs. David Watson, PhD, Psychology, James Torner, PhD, Epidemiology, Arthur Hartz, PM, PhD, Family Medicine, Caroline Carney, MD, Internal Medicine/Psychiatry, Margaret Voelker, MA, a PhD candidate in Epidemiology.

Appendix B. Data Collection Instruments

1. NEUROPSYCHOLOGICAL BATTERY

Test/Item	Abilities assessed
Background Interview	Academic/neurologic history
WAIS-R Similarities	Verbal intellect
WAIS-R Block Design	Nonverbal intellect, visuoconstruction
WAIS-R Digit Span	Concentration, immediate memory span
WAIS-R Digit Symbol	Nonverbal learning, visuomotor speed
NART-R	Premorbid intelligence
COWA	Expressive language, sustained attention
Rey AVLT	Verbal learning and memory
AVLT-Repeated Delay	Exaggeration
BVRT	Immediate visual, memory, exaggeration
RMT	Verbal memory, visual memory, exaggeration
Stroop Test	Response inhibition, concentration
Trail Making Test	Visual scanning, visuomotor speed, cognitive shifting
Starry Night Test	Reaction time, sustained visual attention
Grooved Pegboard Test	Manual dexterity, visuomotor integrity
MMPI-2	Psychological status, exaggeration

NART-R = National Adult Reading Test-Revised; COWA = MAE Controlled Oral Word Association Test; Rey AVLT = Rey Auditory Verbal Learning Test; BVRT = Benton Visual Retention Test; RMT = Warrington Recognition Memory Test; MMPI-2 = Minnesota Multiphasic Personality Inventory-2.

Appendix B. Data Collection Instruments (continued)

2. MENTAL HEALTH EXAMINATION

Instrument	How Administered	Assesses
SCID-IV	rater	Axis I disorders
GAS	rater	Global function
BLSQ	self-report	Life Stress
IBQ	self-report	Hypochondriacal behavior
Mississippi Scale	self-report	PTSD symptom severity, effects
SPS	self-report	Social support
MASQ	self-report	Mood and Anxiety
SNAP	self-report	Personality

SCID-IV = Structured Clinical Interview for DSM-IV Non-Patient Version; GAS = Global Assessment Scale; BLSQ = Brief Life Stress Questionnaire; IBQ = Illness Behavior Questionnaire; SPS = Social Provisions Scale; MASQ = Mood and Anxiety Symptom Questionnaire; SNAP = Schedule of Nonadaptive and Adaptive Personality

Appendix B. Data Collection Instruments (continued)

3. PATIENT EVALUATION

Instrument	How Administered	Evaluation
History and Physical form	Clinician	History and Physical
Review of Systems form	Clinician	Review of Systems
Family History form	Clinician	Family History
SF-36	Self-report	Health Status
HUI or QWB	Self-report	Health Status, Utility Measure
Occupational Exposure questionnaire	Self-report	Occupational Exposure

HUI = Health Utilities Index; QWB = Quality of Well Being scale