AWARD NUMBER: **W81XWH-17-1-0457**

TITLE: **Glutamate Neuroexcitotoxicity in GWI**

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CONTRACTING ORGANIZATION: **American University**
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REPORT DATE: **Sept2019**

TYPE OF REPORT: **Annual**

PREPARED FOR: **U.S. Army Medical Research and Materiel Command**
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: **Approved for Public Release;**
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
SEP2019	Annual	1 Sep 2018 - 31 Aug 2019

4. TITLE AND SUBTITLE

Glutamate Neuroexcitotoxicity in GWI

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-17-1-0457

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The objective of the proposed research is to examine whether dietary exposure to food additives containing glutamate may be contributing to symptoms in Gulf War Illness (GWI). The rationale for proposed study comes from data in the fibromyalgia field which suggests that reducing the consumption of dietary glutamate can reduce over-excitation in the nervous system, leading to symptom improvement. Since there is almost complete symptom overlap between fibromyalgia and GWI, it is of utmost importance to test this diet as a low-cost treatment option in GWI patients. Thus far, we have enrolled 38 subjects into the study and have 2 more people scheduled for their initial visit this month. Overall, we are still on pace to recruit a total of 40 subjects in the timeline indicated in our SOW.

15. SUBJECT TERMS Gulf War Illness, GWI, glutamate, diet, nutrition, intervention					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified	Unclassified		19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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INTRODUCTION: This is phase II clinical trial being completed to examine the effect of using a low glutamate diet as a low-cost treatment option for Gulf War veterans who are suffering from Gulf War Illness (GWI). We are recruiting 40 subjects from across the US who are currently suffering from symptoms according to the Kansas City criteria for GWI. We have completed the second year of the 3-year grant and are on target to complete enrollment on time according to our SOW.

KEYWORDS: Gulf War Illness, GWI, multi-symptom illness, neurological symptoms, glutamate, diet, intervention, nutrients, nutrition

ACCOMPLISHMENTS: We currently have 38 people enrolled in the study, 34 people have completed their participation, and we have scheduled 2 additional subjects to be enrolled this month. Overall, we are accomplishing our goal of timely recruitment in the first year of the study. All participants should be done with their participation by January 2020.

What were the major goals of the project?

The major goals of the project for year 2, as stated in the approved SOW, included:

1. Recruiting, scheduling, and collecting data, diet training, challenge period data collection, and data entry.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1. Major Activities – recruiting subjects, diet training, challenge period, collecting data, and data entry have been achieved over the year. We currently have 38 people recruited and our target enrollment on the SOW was 35 participants, so we are ahead of schedule. Data has been entered for the 34 subjects who have completed their participation and some preliminary analysis has been done for this report.
2. Specific Objectives – our objective was to recruit 35/40 subjects by the end of year 1.
3. Significant Results - thus far, we have enrolled 38 subjects, so we are slightly ahead of schedule for recruitment.

   Due to the second part of the study being a double blind, placebo controlled, crossover challenge, we cannot yet look at that data. However, below is some preliminary data on the improvements we are seeing when comparing baseline to post-diet measures for the 34 subjects who have completed their study participation. At baseline, subjects are reporting 22 symptoms on average, with an average reduction of 10 symptoms after one month on the diet. The total myalgic score and number of tenderpoints have also been significantly reduced, and the average dolorimetry (the amount of pressure they can withstand before feeling pain) has significantly increased. Table 1 reports the median change in outcome measures after one month on the diet, all of which have been

significant. Figure 1 shows changes in abdominal symptoms after one month on the diet, and Figure 2 shows changes in neurological and other symptoms reported after one month on the diet. Overall, this preliminary data is very promising, and we look forward to analyzing the other measures including EEG and measures of brain glutamate using MRS; as well as analyzing the results of the challenge period.

Table 1. **Changes in Outcome Measures after 1-Month on the Low Glutamate Diet**

N=34	**Pre-Diet**	**Post-Diet**	**P-value***
	Median (IQ Range)		
Total Number of Symptoms	22.0 (8)	12.0 (8)	<0.0001
Number of Tender Points (0-18)	13.0 (7)	10.0 (6)	<0.0001
Myalgic (Pain) Score (0-54)	22.0 (20)	13.0 (9)	<0.0001
Average Amount of Pressure (kgs) Before Pain Onset over 18 Tenderpoints - higher better	15.9 (10.6)	19.6 (9.3)	0.002
Chalder Fatigue Scale (0-42)	29.0 (15.0)	16.0 (12.5)	<0.0001
N-back Test of Working Memory (% correct)	62.9 (41)	71.4 (29)	0.008
Neurocognition Index (NCI) - higher is better	97.0 (26)	101.5 (22)	0.028
Processing Speed - higher is better	100.5 (27)	105.0 (24)	0.032
Psychomotor Speed	94.5 (20)	95.5 (22)	0.008
Motor Speed	90.0 (20)	93.5 (77)	0.013
Depression (CES-D) Measure (0-60)	27.0 (22.0)	18.0 (14.5)	<0.0001
Anxiety (GAD-7) Measure (0-21)	8.0 (11.5)	4.0 (8.50)	0.004
PTSD (PCL-C) Measure (0-85)	57.0 (33.0)	39.0 (32.5)	<0.0005
Epworth Sleepiness Scale (ESS)**	12 (7)	8 (7)	0.053
Quality of Life (SF-36) - higher is better			
Physical	40.0 (35.0)	60.0 (37.5)	0.002
Emotional	56.0 (44.0)	76.0 (30.0)	0.0003
Energy	20.0 (35.0)	35.0 (40.0)	0.002
General Health	25.0 (25.0)	35.0 (30.0)	0.004

*Wilcoxon Signed Rank Test **Measure added late, N=15

Figure 1. Comparison of the percentage of GW veterans reporting each gastrointestinal symptom pre- versus post-diet.

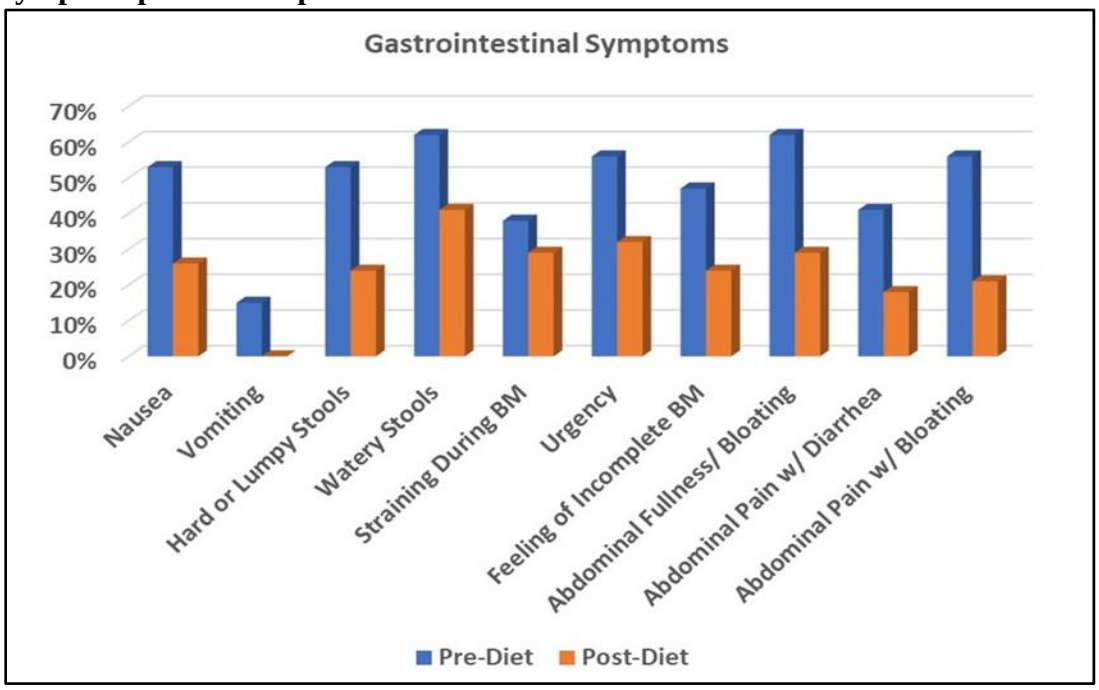
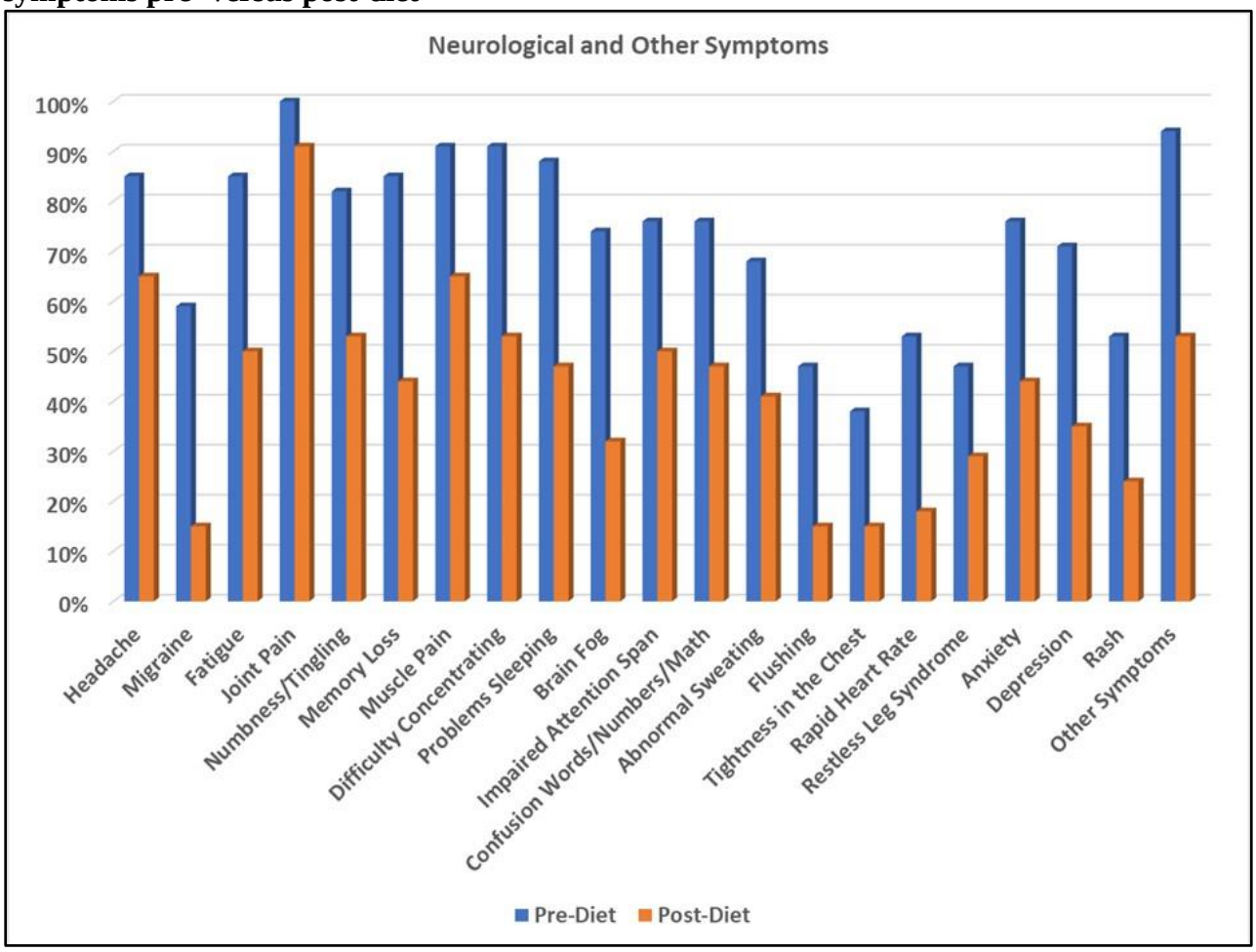


Figure 2. Comparison of the percentage of GW veterans reporting neurological and other symptoms pre- versus post-diet



What opportunities for training and professional development has the project provided?

The project was not intended to provide training and professional development opportunities; however, it has provided many learning opportunities for students in the lab. Two students will be getting the opportunity to present some preliminary data from the study at an upcoming international conference.

How were the results disseminated to communities of interest?

Nothing to report yet.

What do you plan to do during the next reporting period to accomplish the goals?

By January 2020 we should have all subjects finished with their participation and the follow-up period will be complete by March 2020. All data will be entered, and full analyses of all data will be completed. Manuscripts will be written and submitted for publication, and results will be presented at conferences. A lay description of the study results will also be sent to all study participants

IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to report yet.

CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

We experienced a delay due to Georgetown University upgrading their MRI machine. The imaging lab was closed at the beginning of the fiscal year to do the upgrade, which limited our ability to schedule subjects during this time. However, the delay did not keep us from achieving our goals for the year.

Changes that had a significant impact on expenditures

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report for any of the below items.

Significant changes in use or care of human subjects

Significant changes in use or care of vertebrate animals.

Significant changes in use of biohazards and/or select agents

PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

Publications, conference papers, and presentations
Nothing to Report.

Journal publications. Nothing to Report.

Books or other non-periodical, one-time publications. Nothing to Report.

Other publications, conference papers, and presentations. Nothing to Report.

Website(s) or other Internet site(s)
Not applicable.

Technologies or techniques
Nothing to Report.

Inventions, patent applications, and/or licenses
Nothing to Report.

Other Products
None.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Kathleen Holton, PhD, MPH
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0003-2619-7983
Nearest person month worked:	5
Contribution to Project:	Oversight of all aspects of the study.
Funding Support:	

Name:	James Baraniuk, MD
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Medical oversight for safety of participants during challenges.
Funding Support:	

Name:	John VanMeter, PhD
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Oversight of collection of MRI and MRS data for the study.
Funding Support:	

Name:	Elizabeth Brandley, MS (see explanation below)
Project Role:	Research Coordinator Position
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Marketing, recruitment, scheduling, data management
Funding Support:	

Name:	Meissa Jones, MS
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Marketing and Outreach Coordinator
Funding Support:	

Name:	Anna Kirkland
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Collecting data during subject visits, data entry and preliminary data analysis
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

No

What other organizations were involved as partners?

Organization Name: Georgetown University

Location of Organization: Washington, DC

Partner's contribution to the project includes medical oversight for the challenges and collection of MRI data for the study.

Financial support;

In-kind support None

Facilities MRI facility is used.

Collaboration Both Co-Is work at GU.

Personnel exchanges None.

Other. None.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable.

QUAD CHARTS: I was told that this does NOT need to be included.

APPENDICES: None.