

AWARD NUMBER: W81XWH-15-2-0059

TITLE: Targeted Alteration of Dietary Omega-3 and Omega-6 Fatty Acids for the Treatment of Post-Traumatic Headaches

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REPORT DATE: October 2016

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;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE October 2016		2. REPORT TYPE Annual		3. DATES COVERED 30 Sep 2015 - 29 Sep 2016	
4. TITLE AND SUBTITLE Targeted Alteration of Dietary Omega-3 and Omega-6 Fatty Acids for the Treatment of Post-Traumatic Headaches				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-15-2-00	
				5c. PROGRAM ELEMENT NUMBER 59	
6. AUTHOR(S) Kimbra Lou Kenney, M.D. E-Mail: Kimbra.kenney@usuhs.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. 6720-A Rockledge Drive Bethesda, MD 20817				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 Post-traumatic headache (PTH) is a common problem in military personnel due to their high rate of traumatic brain injury (TBI). From a prior study in migraine we demonstrated that a high Omega-3/low Omega-6 (H3-L6) diet intervention reduced headache pain, altered circulating anti- and pro-nociceptive lipid mediators and their precursor fatty acids, reduced psychological distress and improved quality-of-life in a chronic headache population. We propose to carry out a 2-arm, parallel group, randomized, controlled 12-week dietary intervention trial to evaluate the biochemical effects and therapeutic efficacy of two dietary interventions (one high in Omega-3 and the other high in Omega-6, reflecting the usual US diet) in patients with PTH that are migrainous. We hypothesize that compared to the Control Diet (high Omega-6, low Omega-3), the H3-L6 intervention will produce significant increases in anti-nociceptive n-3 metabolites including 17-hydroxy DHA (Primary Biochemical Aim), and reductions in pro-nociceptive n-6 metabolites. Further, we hypothesize that compared to the Control Diet, the H3-L6 intervention will produce significant improvement in the Headache Impact Test—a headache-specific quality of life measure-Primary Clinical Outcome), mean total Headache Hours per day, and mean Severe Headache Hours per day.					
15. SUBJECT TERMS Post-traumatic headache (PTH), traumatic brain injury (TBI), nociceptive neurotransmission, migraine, chronic inflammation, biomarker, Omega-3, Omega-6, Headache Impact Test (HIT), nutritional intervention					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 11	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

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1. INTRODUCTION:

Post-traumatic headache (PTH), a common and debilitating secondary headache disorder, is a common problem in military personnel due to their high rate of traumatic brain injury (TBI). Most PTHs have a phenotype indistinguishable from primary headache disorders and have similar responses to therapy. Recent studies indicate that migraine is the most common headache type after trauma, accounting for 50-60% of all PTH, while tension-type headaches account for less than 20%. The mechanisms of PTH are complex and incompletely understood but recent studies emphasize the role of inflammation, cytokine modulation, microglial activation, and abnormalities in neurotransmitter activity in mediating PTH. These observations provide one mechanism underlying the proposed use of dietary interventions designed to reduce chronic inflammation and promote anti-nociceptive neurotransmission, and biomarker data we will obtain will provide direct support for the role of inflammation in PTH. From a prior study in migraine we have preliminary data demonstrate that a high Omega-3/low Omega-6 (H3-L6) diet intervention reduced headache pain, altered circulating anti- and pro-nociceptive lipid mediators and their precursor fatty acids, reduced psychological distress and improved quality-of-life in a chronic headache population. These compelling preliminary data also help establish the feasibility of implementing this dietary intervention in TBI populations with chronic pain. We propose to carry out a 2-arm, parallel group, randomized, controlled 12-week dietary trial to evaluate the biochemical effects and therapeutic efficacy of two dietary interventions (one high in Omega-3 and the other reflecting the usual US diet, high in Omega-6) in patients with PTH with migrainous phenotype. We hypothesize that compared to the Control Diet (high Omega-6, low Omega-3), the H3-L6 intervention will produce significant increases in anti-nociceptive n-3 metabolites including 17-hydroxy DHA (Primary Biochemical Aim), and reductions in pro-nociceptive n-6 metabolites. Further, we hypothesize that compared to the Control Diet, the H3-L6 intervention will produce significant improvement in the Headache Impact Test—a headache-specific quality of life measure-Primary Clinical Outcome); mean total Headache Hours per day; and mean Severe Headache Hours per day.

2. KEYWORDS: Provide a brief list of keywords (limit to 20 words).

Post-traumatic headache (PTH), traumatic brain injury (TBI), nociceptive neurotransmission, migraine, chronic inflammation, biomarker, Omega-3, Omega-6, Headache Impact Test (HIT), nutritional intervention

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Task 1: Planning and Regulatory Review (Months 1-5)

Subtask 1a. Complete the detailed protocol, Standard Operating Procedures (SOP) manual, develop Case Report Forms (CRFs), create and beta test Database, create study website. Trial registration in Clinicaltrials.gov. Advertise for and hire study staff.

Subtask 1b. Obtain IRB approvals at WRNMMC, USUHS, NIH, UNC-Chapel Hill, and Womack Army Medical Center.

Subtask 1c. Training of dietitians, and standardize preparation of diets.

Subtask 1d. Training of study staff at all sites.

Subtask 1b has not yet been obtained due to significant WRNMMC IRB delays

Task 2. Start recruitment and enrollment of patients at all sites (Months 6-12)

Subtask 2a. Target is that all sites will have enrolled at least 1 participant by the end of Year 1.

Target is that all sites combined have enrolled at least 20 participants.

Subtask 2b. All sites will have had 1 monitoring visit to insure adherence to protocol and that all study procedures are being carried out uniformly and efficiently.

2c. At the end of Year 1, biochemical assays on participants enrolled over the first 6 months will insure that sample quality is excellent and that anticipated values are obtained.

Task 3. Continue patient recruitment and enrollment (Months 13-24)

Subtask 3a. Anticipate that at the end of Year 2, 70 participants will have been enrolled at the three clinical sites.

Subtask 2b. Once enrollment is active at each site, monitoring visits q 6 months to insure adherence to the protocol and that all study procedures are being carried out uniformly and efficiently.

2c. Complete biochemical assays on participants enrolled in the first half of the study. Prepare first manuscript for publication on the association of baseline PTH characteristics with plasma levels of bioactive

Task 4. Continue patient recruitment and enrollment (Months 25-36)

Subtask 3a. Anticipate that at the end of Year 3 110 participants will have been enrolled at the three clinical sites.

Subtask 2b. Continue monitoring visits q 6 months to insure adherence to the protocol and that all study procedures are being carried out uniformly and efficiently.

Subtask 2c. Complete biochemical assays on participants enrolled in the first three years of the study. Prepare second manuscript for publication on the association of baseline post-concussive symptoms, mood, affective, and cognitive problems, and plasma levels of bioactive lipids.

Task 5. Complete all study procedures (Months 36-40)

Subtask 5a. Complete enrollment of 120 participants, including followup after 12 weeks of dietary intervention.

Subtask 5b. Resolve all data queries originating from data monitoring visits.

Subtask 5c. Complete biochemical assays for entire study.

Task 6. Data analysis and preparation of primary manuscripts. (Months 40 – 48)

Subtask 6a. Complete data cleanup and database lock.

Subtask 6b. Complete analysis of primary and secondary outcomes.

6c. Prepare manuscripts for publication for primary outcome and secondary outcomes.

What was accomplished under these goals?

1. Prepared WRNMMC protocol package for scientific review (a requirement for full IRB submission) and received WRNMMC scientific review committee approval letter 7-9-2015
2. Prepared full WRNMMC protocol package and submitted for initial administrative review by WRNMMC IRB, 24 AUG 2015
3. IRBNet discontinued at WRNMMC IRB and announcement of IRB delays at WRNMMC with anticipated delays of > 6 months for reviews/approvals.
4. Received WRNMMC administrative review stipulations, 30 OCT 2015
5. Resubmitted protocol package addressing administrative pre-review stipulations, 25 NOV 2015
6. WRNMMC IRB administrative preview completed and approved 3 DEC 2015
7. Protocol package forwarded for WRNMMC IRB expedited review 8 DEC 2015.
8. Received full WRNMMC parent/shell multi-site protocol approval 16 FEB 2016

9. UNC Collaborators received local protocol approval by UNC IRB 23 FEB 2016
10. Submitted WRNMMC parent protocol amendment to add WAMC as a third site 8 MAR 2016 and approved 30 MAR 2016
11. Submitted site-specific addendum amendment for WRNMMC 9 APR 2016 and review never initiated before eIRB, IRIS, went live at WRNMMC and submission never reviewed.
12. NIH collaborators submitted and received local IRB exempt status as they are conducting de-identified specimen analysis only for this project 3 JUN 2016.
13. The FDA ruled that an IND is not required for the study and that the protocol is exempt from IND requirements 24 JUN 2016 with exempt letter dated 28 JUN 2016.
14. Submitted WRNMMC parent protocol, NIH IRB waiver, FDA IND waiver and UNC approved protocol to HRPO for second level approval. This is currently pending the 3 SSA modification approval letters for WRNMMC.
15. Amendment for Site-Specific Addendum (SSA) submitted for WRNMMC as a performance site 9 APR 2016 to WRNMMC IRB with administrative review pending in JUN 2016
16. The DoD eIRB, IRIS, went live 25 APR 2016 and instruction for submission of SSA for multi-site studies was in flux but clarified by WRNMMC Director of IRB in mid JUN 2016 instructing that each of the 3 enrolling MTF sites should submit a single modification package with a single uploaded protocol including site-specific protocol information for all 3 sites in one protocol template and 3 separate site-specific consent forms (each based on the approved parent multi-site protocol and consent approved 16 FEB 2016, but with local specifics/modifications), along with supporting forms for study-related staff at each site. This submission was not possible until IRIS went live at WAMC in AUG 2016. The submission was reviewed and approved at FBCH and was forwarded to WRNMMC 5 OCT 2016 for final review/approval, which remains pending at the time of this annual report.
17. A CRADA has been established between WRNMMC and HJF for the study at WRNMMC.
18. An overall study coordinator has been hired for the study.
19. A subcontract is in process of being established for database management and electronic transfer to FITBIR.
20. A DSMB with stoppage rules has been established and approved by the UNC IRB.
21. Identified study personnel for hire, including a research dietician and research assistant at WRNMMC, and study coordinators at WAMC and WRNMMC.
22. Hiring a dietician and research assistant at FBCH
23. Held monthly conference calls to plan personnel, food and assay integrity for study.
24. Purchasing assay equipment for NIH fat metabolite assays.
25. Identified food storage requirements at each study site and purchasing food freezers
26. Established a web-based headache diary and randomization system for the study at NIH.
27. Change of overall grant PI from Ramon Diaz-Arrastia MD PhD to Kimbra Kenney MD.

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

The research dietician at UNC-Chapel Hill, the head dietician for the study, will train the dieticians at each of the other sites. There is a site visit scheduled for early November at UNC for the dieticians and study RAs to see a similar study in process. Additionally, training videos and reviews of dietary sessions are scheduled between the head study dietician and the dietician at each site.

How were the results disseminated to communities of interest?

Nothing to Report.

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

Work with WRNMMC to expedite final multi-site review. We are already working with the primary reviewer at HRPO to expedite secondary review.

4. **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.

5. **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

As noted earlier in this annual report and prior quarterly reports, there has been a significant delay in getting IRB approvals for this study through the multi-site study IRB process since the termination of IRBNet last fall, intervening local processes and non-uniform launch of IRIS at the 3 performance study sites for this protocol. This has significantly delayed launching of this study. The WRNMMC IRB initially suggested a 6 month delay; this will likely result in a 9 month delay for our multi-site study. We do not anticipate further study delays once we have full regulatory approvals in place, but cannot be certain at the time of this writing how long it will delay the launching of the study.

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

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals.

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. 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**
Report only the major publication(s) resulting from the work under this award.

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)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Kimbra Kenney MD
Project Role:	Grant PI
Nearest person month worked:	1.2
Contribution to Project:	Dr. Kenney assumed role of PI and directed development and submission of protocol through the WRNMMC multi-site eIRB, IRIS
Funding Support:	HJF through 31 May 2016 and DoD civilian employee from 1 June 2016
Name:	Keturah Faurot PA, PhD
Project Role:	UNC AI
Nearest person month worked:	2
Contribution to Project:	Dr. Faurot developed and submitted UNC protocol, established study DSMB and developed CRFs for the study
Funding Support:	HJF

Name: Chris Ramsden MD
Project Role: NIH PI
Nearest person month worked: 1.2
Contribution to Project: Dr. Rasmden developed submission of exempt protocol through the NIH IRB
Funding Support: Federal employee

Name: Wesley Cole, PhD
Project Role: WAMC PI
Nearest person month worked: 1
Contribution to Project: Dr. Cole developed and submitted WAMC protocol,
Funding Support: HJF

Name: Maulik Purohit MD
Project Role: FBCH PI
Nearest person month worked: 0.5
Contribution to Project: Dr. Purohit developed and submitted FBCH protocol
Funding Support: Federal employee

Name: Beth MacIntosh
Project Role: UNC AI and study dietician
Nearest person month worked: 1
Contribution to Project: Ms MacIntosh assisted with dietician portions of study protocols, participated in monthly conference calls, and is training study dieticians
Funding Support: HJF

Name: Carol Moore MA
Project Role: USUHS AI and Senior Study Manager
Nearest person month worked: 2
Contribution to Project: Ms Moore assumed primary role of protocol submission and WRNMMC IRB navigation
Funding Support: HJF

Name: Cora Davis, BA
Project Role: USUHS AI and Research Assistant
Nearest person month worked: 1
Contribution to Project: Assisted Ms Moore in protocol submission and navigation
Funding Support: HJF

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

Nothing to Report.

As noted earlier, there has been a change of the USUHS PI from Ramon Diaz-Arrastia MD PhD to Kimbra Kenney MD; this has been approved by USUHS and the funding source.

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: NA

QUAD CHARTS: NA

9. APPENDICES: NA