AD_____
(Leave blank)

Award Number: DOD Award W81XWH-08-2-0068

TITLE: A Randomized Controlled Trial of Medical Therapies for Chronic Post-Traumatic Headaches

PRINCIPAL INVESTIGATOR: Jay Erickson, MD, PhD, LTC US Army

CONTRACTING ORGANIZATION: Henry M. Jackson Foundation
Rockville, MD 20852

REPORT DATE: May 2010

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: (Check one)

X Approved for public release; distribution unlimited

☐ Distribution limited to U.S. Government agencies only; report contains proprietary information

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
1 May 2010	Annual	1 MAY 2009-30 APR 2010

4. TITLE AND SUBTITLE

A Randomized Controlled Trial of Medical Therapies for Chronic Post-Traumatic Headaches

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-08-2-0068

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Jay Erickson, M.D., Ph.D.

E-Mail: jay.erickson@us.army.mil

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

Henry M. Jackson Foundation
Rockville, MD 50852

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

A randomized, placebo-controlled clinical trial is being conducted to evaluate the effectiveness of propranolol, topiramate, and amitriptyline as treatments for chronic post-traumatic headaches secondary to combat-related mild head injury. The study is in the first of three years. 34 of 240 subjects have been enrolled. The study medications are well tolerated. Study subjects had a 60% decrease in headache frequency after 3 months of treatment. There is insufficient data at this time to draw conclusions about the efficacy of specific study medications. The study remains open to enrollment.

15. SUBJECT TERMS
Headache, mild head trauma, treatment

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	6	19b. TELEPHONE NUMBER *(include area code)*

Introduction

Headaches are the most common symptom after mild traumatic brain injury (1-4). Chronic post-traumatic headaches (PTHAs) develop in 20% of TBI victims, contributing to disability, healthcare utilization, and poor quality of life (5-6). There are no prospective, controlled clinical trials evaluating medical treatments for chronic post-traumatic headaches (7). The purpose of this study is to determine the effectiveness of propranolol, amitriptyline, and topiramate as treatments for chronic PTHAs. We are conducting a single-center, prospective, randomized, double-blind, placebo-controlled, multi-arm trial to evaluate propranolol, amitriptyline, and topiramate for treatment of chronic PTHAs. A total of 240 patients meeting International Classification of Headache Disorders (ICHD) diagnostic criteria for chronic post-traumatic headaches will be enrolled. Subjects are recruited from the Traumatic Brain Injury Program and the Neurology Clinic at Madigan Army Medical Center, Ft. Lewis, WA. Study participants are U.S. Army soldiers with chronic post-traumatic headaches attributable to mild traumatic head injury sustained while deployed to a combat theater. Participants are randomized to receive placebo, propranolol 80 mg daily dose, amitriptyline 50 mg daily dose, or topiramate 100 mg daily dose for 3 months. The primary outcome measure is the number of moderate-severe headache days during the third month of treatment. Secondary outcome measures include the proportion of subjects with at least a 50% reduction in headache frequency, headache-related disability as measured by the Headache Impact Test and Migraine Disability Assessment Scale, PTSD symptom checklist score, and medication side effects. The findings of this study will improve the care of patients with chronic headaches after traumatic brain injury.

Body:

As of May 1, 2010, 282 patients have been screened for study enrollment and 46 patients have been enrolled. In the last year, 10 patients were enrolled. Study outcome measures have been obtained on 33 subjects. 13 patients disenrolled prior to study outcomes being obtained. The most common reason for a subject disenrolling was that he moved away from the geographic region.

Interval analysis of blinded data in 33 subjects showed that headache frequency decreased from a mean of 10.9 days per month during the baseline month to 6.3 days per month during the third

month of treatment (see graph). This is a 42% decline in headache frequency. These data are consistent with our hypothesis and suggest that one or more of the study treatments may be having a beneficial effect on headaches. There are too few subjects in each treatment arm to compare the outcomes of different treatments at this time.

The study medications have been well tolerated. One patient temporarily discontinued study medication after experiencing mild sedation, but was able to re-start medication and complete study participation. No serious adverse events have occurred.

The study remains open to enrollment. Enrollment was slow over the last year because most combat troops at Ft. Lewis were deployed. The enrollment rate is expected to increase sharply starting in June 2010 when three brigade of troops return to Ft. Lewis. Our goal is to enroll 12 patient per month for the next 12 months. The duration of the study will likely need to be extended to complete enrollment.

Key Research Accomplishments:

1. The study protocol was approved by the IRB in 2008.
2. A research P.A. was hired and trained in 2008-09.
3. The investigational pharmacy procured identical-appearing study medications and placebo capsules, and developed a system for randomizing, labeling, dispensing, and monitoring study pills.
4. The study has enrolled 46 of 240 subjects.
5. A study database has been generated.
6. The study continues to enroll new subjects.
7. Interval analysis of blinded data shows overall improvement of headaches, good tolerability of study medications, and no serious adverse events.

Reportable Outcomes:

There are no reportable outcomes at this time.

Conclusion:

This clinical trial is evaluating the effectiveness of three prophylactic medications for chronic post-traumatic headaches. The study is now 19% complete with 46 out of 240 subjects enrolled. There is insufficient data at this time to draw meaningful conclusions about the efficacy of specific study medications. However, interval data analysis has shown an overall 42% improvement in headache frequency among study participants. The study medications have been well tolerated without any serious adverse events. Study enrollment is expected to increase sharply throughout the next year when over 15,000 troops return to Ft. Lewis. The study may need to be extended beyond past May 2011 in order to enroll all 240 subjects.

References:

1. Packard RC. Epidemiology and pathogenesis of posttraumatic headaches. J Head Trauam Rehabil 1999;14: 9-21.
2. Uomoto JM, Esselman PC. Traumatic brain injury and chronic pain: differential types and rates by head injury severity. Arch Phys Med Rehabil 1993;74: 61-64.
3. Lahz S, Bryant RA. Incidence of chronic pain following traumatic brain injury. Arch Phys Med Rehabil 1996;77: 889-891.
4. Walker WC, Seel RT, Curtiss G, Warden DL. Headache after moderate and severe traumatic brain injury: a longitudinal analysis. Arch Phys Med Rehabil 2005;86:1793-1800.
5. Packard RC, Ham LP. Posttraumatic headache: determining chronicity. Headache 1993;33: 133-4.
6. Baandrup L, Jensen R. Chronic post-traumatic headache- a clinical analysis in relation to the International Headache Classification 2nd edition. Cephalalgia 2005;25: 132-138.
7. Lew HL, Lin PH, Fuh JL, Wang SJ, Clark DJ, Walker WC. Characteristics and treatment of headache after traumatic brain injury: A focused review. Am J Phys Med Rehabil 2006;85:619-627.

Supporting Data:

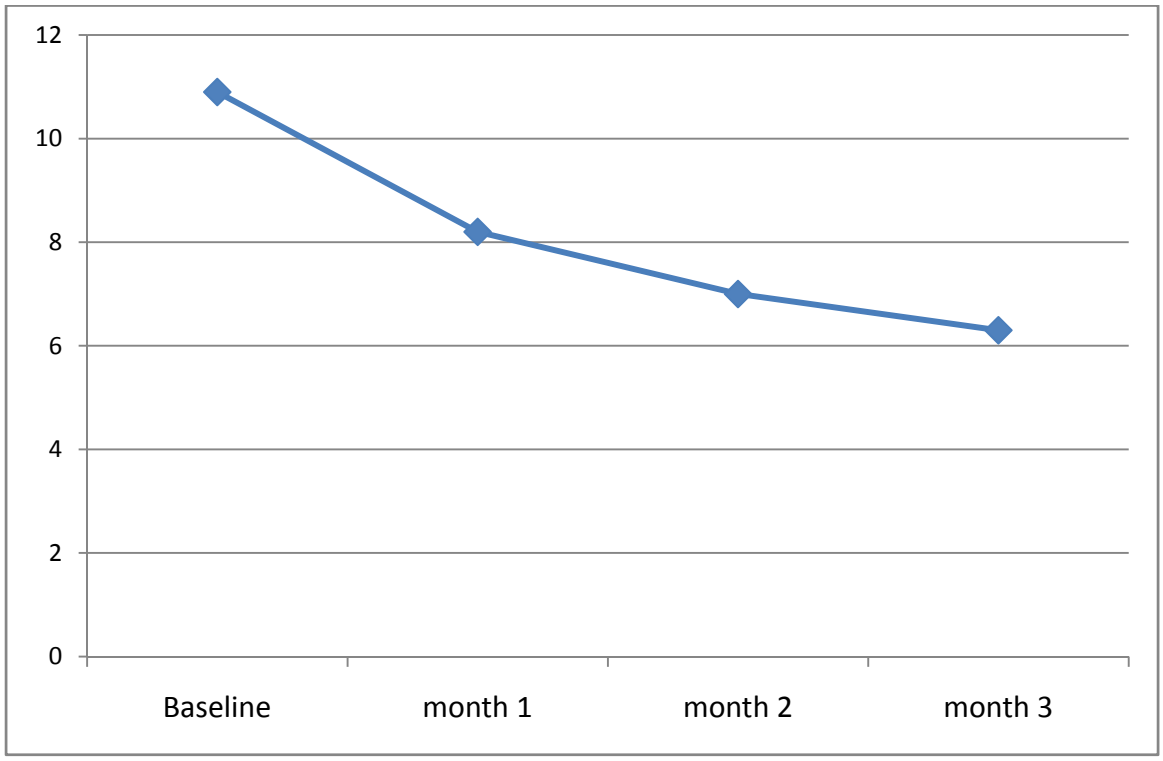

Figure 1. Monthly frequency of moderate-severe headaches among the first 33 subjects with available outcome data.

Appendices: none