

AD _____

Award Number: W81XWH-08-2-0068

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

PRINCIPAL INVESTIGATOR: Dr. Jay Erickson

CONTRACTING ORGANIZATION: The Henry M. Jackson Foundation for the Advancement of
Military Medicine
Rockville, MD 20652

REPORT DATE: December 2011

TYPE OF REPORT: Final

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

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) 01-12-2011		2. REPORT TYPE Final		3. DATES COVERED (From - To) 1 MAY 2008 - 30 Nov 2011	
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) Dr. Jay Erickson 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) The Henry M. Jackson Foundation for the Advancement of Military Medicine Rockville, MD 20652				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, double-blinded, placebo-controlled clinical trial was conducted to evaluate the effectiveness of propranolol, topiramate, and amitriptyline as treatments for chronic post-traumatic headaches secondary to combat-related mild head injury. Over a 3-year period 305 soldiers with chronic PTH were screened and 64 were enrolled, falling short of the enrollment target of 240 subjects. 39 (61%) had evaluable data after drug titration and 34 (53%) completed the 3-month treatment period. Discontinuation rates ranged from 39% for topiramate to 53% for amitriptyline but were not significantly different between treatment arms. Monthly headache days decreased from 12.2 at baseline to 7.9 during the final month in all subjects (-36%, p=0.0001), 16.7 to 8.7 in the placebo arm (-48%, p=0.012), 11.7 to 6.1 in the amitriptyline arm (-41%, p=0.0005), 14.0 to 8.3 in the propranolol arm (-41%, p=0.10), and 9.3 to 8.8 in the topiramate arm (-5%, p=0.80). Mean MIDAS scores decreased from 71 at baseline to 31 at the final visit among all subjects (p=0.0001) and significantly declined in the placebo, topiramate, and propranolol arms. There were no significant differences between placebo and any treatment. PTSD symptom checklist scores significantly declined in the topiramate arm. This study is limited by the small number of subjects, high response rate in the placebo arm, and relatively low subject completion rate. The study is closed.					
15. SUBJECT TERMS Headache, mild head trauma, concussion, treatment, clinical trial					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			USAMRMC
			UU	8	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	2
Body.....	2
Key Research Accomplishments.....	3
Reportable Outcomes.....	3
Conclusion.....	3
References.....	4
Supporting Data.....	5
Appendices.....	6

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 was to determine the effectiveness of propranolol, amitriptyline, and topiramate as treatments for chronic PTHAs. We conducted a single-center, prospective, randomized, double-blind, placebo-controlled, multi-arm trial to evaluate propranolol, amitriptyline, and topiramate for treatment of chronic PTHAs. The enrollment target was 240 patients meeting International Classification of Headache Disorders (ICHD) diagnostic criteria for chronic post-traumatic headaches. Subjects were recruited from the Traumatic Brain Injury Program and the Neurology Clinic at Madigan Army Medical Center, Ft. Lewis, WA. Study participants were U.S. Army soldiers with chronic post-traumatic headaches attributable to mild traumatic head injury sustained while deployed to a combat theater. Participants were 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 was the number of moderate-severe headache days during the third month of treatment. Secondary outcome measures included the proportion of subjects with at least a 50% reduction in headache frequency, headache-related disability as measured by the Headache Impact Test (HIT-6) and Migraine Disability Assessment Scale (MIDAS), PTSD symptom checklist score, and medication tolerability. The findings of this study will improve the care of patients with chronic headaches after traumatic brain injury.

Body:

Over the 3.5-year study period, 305 soldiers were screened for study enrollment and 64 were enrolled. Of these, 39 (61%) had evaluable data after drug titration and 34 (53%) completed the 3-month treatment period. Discontinuation rates ranged from 39% for topiramate to 53% for amitriptyline but were not significantly different between treatment arms. The most commonly identified reason for a subject discontinuing the study was that he moved away from the geographic region. No serious adverse events occurred.

Monthly headache days decreased from 12.2 at baseline to 7.9 during the final month in all subjects (-36%, $p=0.0001$), 16.7 to 8.7 in the placebo arm (-48%, $p=0.012$), 11.7 to 6.1 in the amitriptyline arm (-41%, $p=0.0005$), 14.0 to 8.3 in the propranolol arm (-41%, $p=0.10$), and 9.3 to 8.8 in the topiramate arm

(-5%, $p=0.80$). $\geq 50\%$ responder rates were 49% (19/39) for all subjects, 50% (3/6) for placebo, 67% (8/12) for amitriptyline, 44% (4/9) for propranolol, and 33% (4/12) for topiramate. Responder rates were 49% (19/39) for all subjects, 50% (3/6) for placebo, 67% (8/12) for amitriptyline, 44% (4/9) for propranolol, and 33% (4/12) for topiramate. Mean MIDAS scores decreased from 71 at baseline to 31 at the final visit among all subjects ($p=0.0001$) and significantly declined in the placebo, topiramate, and propranolol arms. HIT-6 scores and PTSD symptom checklist scores significantly declined in the topiramate arm only.

Key Research Accomplishments:

1. 64 subjects were enrolled, randomized, started on one of the study medications, and monitored for follow-up outcomes.
2. Follow-up of all enrolled study subjects was completed. The study is closed.
3. A study database was generated and analyzed.
4. An abstract reporting the study findings was accepted for presentation at the 2012 American Academy of Neurology meeting in April, 2012.

Reportable Outcomes:

1. An abstract of the study findings has been accepted for presentation at the 2012 American Academy of Neurology meeting in April, 2012.
2. Erickson JC, Neely E, Theeler BJ. Post-traumatic Headache. *Continuum: Lifelong Learning in Neurology*. December, 2010; Vol 16(6):55-78. (8)

Conclusion:

This study is limited by the small sample size and unexpectedly high response rate in the placebo arm. Amitriptyline, propranolol, and topiramate were similarly tolerated and were associated with significant improvements in headache frequency and/or headache-related disability but no treatment was superior to placebo. Topiramate was also associated with a significant improvement in PTSD symptoms. The slow enrollment rate of subjects and the high discontinuation rate (47%) reveal significant challenges in conducting a 4-month study in military service members. The findings will be useful for designing large, multi-center clinical trials to conclusively evaluate the efficacy of headache prophylactic therapies for chronic PTH in military personnel.

References:

1. Packard RC. Epidemiology and pathogenesis of posttraumatic headaches. *J Head Trauma 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.
8. Erickson JC, Neely E, Theeler BJ. Post-traumatic Headache. *Continuum: Lifelong Learning in Neurology*. December, 2010; Vol 16(6):55-78.

Supporting Data:

Table 1. Number of subjects in each treatment arm.

Treatment	#Randomized	# completing drug titration	#Completing study
Placebo	12	6 (50%)	6 (50%)
Topiramate	18	12 (67%)	11 (61%)
Propranolol	17	9 (53%)	9 (53%)
Amitriptyline	17	12 (71%)	8 (47%)
All	64	39 (61%)	34 (53%)

Table 2. Responder rates in each treatment arm.

Treatment	Responders ($\geq 50\%$ decrease)
Placebo	3/6 (50%)
Topiramate	4/12 (33%)
Propranolol	4/9 (44%)
Amitriptyline	8/12 (67%)
All	19/39 (49%)

Table 3. Change in monthly headache days.

Treatment	n	Mean Monthly HA days/month (SD)			% Change	Paired t-test
		Baseline	Final	Change		
Placebo	6	16.67	8.67	-8.0	-48%	0.0121
Topiramate	12	9.25*	8.83	-0.42*	-5%	0.80
Propranolol	9	14.0	8.33	-5.67	-41%	0.10
Amitriptyline	12	11.67	6.08	-5.58	-41%	0.0005
All	39	12.23 (6.39)	7.85 (6.21)	-4.38	-36%	0.0001

p=0.01 compared to placebo

Table 4. Headache-related disability as measured by the MIDAS and HIT-6.

Treatment	MIDAS			HIT-6		
	Baseline	Final	paired t	Baseline	Final	paired t
Placebo	83.17	27.83	0.008	63.17	51.33	0.122
Topiramate	62.27	25.00	0.019	61.6	56.5	0.046
Propranolol	68.5	29.13	0.046	64.38	53.5	0.167
Amitriptyline	75.0	45.86	0.21	55.7	52.0	0.32
All (n=32)	70.53(47.8)	31.13(38.28)	0.0001	61.29(5.92)	53.71(13.62)	0.0034

Table 5. Depression symptoms (PHQ-9) and PTSD symptoms (PCL).

Treatment	PHQ-9			PCL		
	Baseline	Final	paired t	Baseline	Final	paired t
Placebo	13.17	10.5	0.39	49.0	45.8	0.63
Topiramate	11.45	9.82	0.55	48.1	38.3	0.0495
Propranolol	10.0	8.75	0.32	42.3	37.1	0.40
Amitriptyline	8.29	8.00	0.87	37.7	36.1	0.66
All (n=32)	10.72(4.84)	9.28(7.06)	0.21	44.2 (16.21)	38.9 (17.75)	0.047

Appendices: none