

AD _____
(Leave blank)

Award Number: W81XWH-08-2-0652

TITLE: *A Double Blind Trial of Divalproex Sodium for Affective Lability and Alcohol Use Following Traumatic Brain Injury*

PRINCIPAL INVESTIGATOR: Thomas P. Beresford, M.D.

CONTRACTING ORGANIZATION: Denver Research Institute
Denver, CO 80220

REPORT DATE: October 2009

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

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			<i>Form Approved</i> 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) 01/10/09		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 15 Sep 2008 - 14 Sep 2009	
4. TITLE AND SUBTITLE <i>A Double Blind Trial of Divalproex Sodium for Affective Liability and Alcohol Use Following Traumatic Brain Injury</i>			5a. CONTRACT NUMBER W81XWH-08-2-0652		
			5b. GRANT NUMBER PT075168		
			5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) Thomas P. Beresford, M.D. Email: Thomas.Beresford@uchsc.edu			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Denver Research Institute VAMC - 151 1055 Clermont St. Denver, CO 80220			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 large and under-recognized sub-set of patients suffer from both traumatic brain injury (TBI) and alcohol abuse/dependence (AA/D). This group appears to use alcohol to self-treat fronto-limbic disinhibition, expressed clinically as affective liability, following TBI. This often results in AA/D and worsens TBI prognosis. The primary study hypothesis states that symptom frequencies of fronto-limbic disinhibition, expressed as affective liability, will decrease significantly in TBI subjects treated with divalproex sodium, a mood stabilizing medication, as compared to placebo. To test the primary hypothesis, we propose an 8 week, double-blind, randomized, controlled trial comparing divalproex sodium to placebo in 50 subjects—25 per group—who suffer from both TBI and AA/D. Subjects will be recruited through the initiating site located at the Department of Veterans Affairs Medical Center, Denver. Final approval from multiple review bodies was granted on September 15, 2009, four months longer than anticipated. Active subject recruitment began on that date. There are no results to report at this time.					
15. SUBJECT TERMS Traumatic Brain Injury, Alcohol Use, Mood, Mood Stabilization					
16. SECURITY CLASSIFICATION OF: U			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 9	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	6
Key Research Accomplishments.....	7
Reportable Outcomes.....	7
Conclusion.....	7
References.....	8
Appendix.....	9

Introduction

Traumatic brain injury (TBI) is highly prevalent in at risk occupations including US service personnel. Of particular concern now are those wounded in combat in Iraq and Afghanistan where TBI appears to account for a larger proportion of casualties than in prior U.S. wars. Reports from Operation Iraqi Freedom (OIF) suggest that as many as one-quarter of personnel injured in combat there suffer TBI. (Okie, 2005) Psychiatric and neurocognitive disorders—especially disorders of mood--have been noted in as many as three-quarters of combatants who suffered TBI in previous conflicts (Lishman, 1973) and are often more adversely affected by emotional problems than by physical disabilities. (Nelson et al., 1998) Although specific data are not at hand, published frequencies suggest that as many as one combat related case of TBI in every five may likely exhibit symptoms related to fronto-limbic disinhibition that is expressed as a poorly controlled, or labile, affect. It is that condition that caught our clinical interest and led to a preliminary research project.

Specifically, the Principal Investigator (PI) observed a clinical population of former service personnel who served in high risk environments such as paratroop units, flight crews, and below decks aboard ship and who had suffered TBI. Common to all was a poorly managed affective irritability or anxiety that began after TBI and was often misdiagnosed as another Axis I psychiatric disorder, usually a mood disorder such as bipolar illness, or schizoaffective illness. Likewise, all of the cases had no such symptoms prior to TBI. This posed a clinical question: How to treat post-TBI affective lability/ fronto-limbic disinhibition?

As a class of agents, anticonvulsant medication appears, empirically, to lessen the affective lability in TBI. Carbamazepine may ameliorate agitation and disinhibited behavior as well as depression and manic symptoms following TBI. (Azouvi et al., 1999; Bakchine et al., 1989; Perino et al., 2001) Valproate may improve post-TBI aggressive behaviors (Wroblewski et al., 1997), episodic explosiveness (Geraciotti, 1994), and bipolar syndrome. (Pope et al., 1988) Affective lability may include poorly controlled expression of mood and anxiety upset. (Arciniegas and Silver, 2001) Other agents, such as benzodiazepines may address similar symptoms, yet these drugs introduce addiction and tolerance issues and do not appear to address specific causes of affective lability.

To complicate matters clinically, the PI saw many cases in the veteran population in which TBI patients had been trying to treat their affectively lability—generally an irritability or anxiety state that interrupted or prevented normal functioning at work or in family life, often leading to broken marriages, job losses, occasionally to homelessness. Unfortunately, the most readily available drug of choice for many TBI victims was often ethyl alcohol. The result of self treatment was frequently the development of an alcohol use disorder that only served to worsen the fronto-limbic disinhibition following the TBI.

Alcohol abuse and/or dependence (AA/D) and mood disturbance often co-occur following TBI. (Corrigan, 1995) In a group of 20 TBI survivors who had evidence of alcohol abuse in the year following their injury, 15 (75%) developed a mood disorder. (Jorge and Robinson, 2002) In a non-alcohol abusing group, only 44% patients developed a mood disorder during the same time period. (Jorge and Robinson, 2002) In persons with AA/D and affective lability following TBI, successful treatment of mood lability may reduce or eliminate drinking behaviors. (Beresford et al., 2005) Following our interests in both alcoholism and TBI, we have accrued clinical experience in recognizing and treating patients who present with mood lability including symptoms of AA/D after TBI. We have observed a similar pattern of decrease in, or cessation of alcohol use following treatment of underlying TBI-induced affective lability. Many AA/D+TBI patients describe their emotional symptoms as contributing to their heavy alcohol

use. Observed clinically, when such cases reach alcohol abstinence, their symptoms of poorly regulated affective expression most often do not appear to be those of an idiopathic mood or anxiety disorder. They do not present the severity or the same natural courses as do Major Depressive Disorder, Bipolar Illness, or Anxiety Disorder, for example. Instead both symptoms and course appear more characteristic of the sustained affective lability often observed following TBI. (Beresford et al., 2005) This suggests that TBI survivors represent a patient group for whom treatment of neuropsychiatric symptoms following TBI may alleviate both TBI-related affective lability and also heavy ethanol use by treating the condition for which ethanol is used.

We believe our clinical observation of excessive alcohol use following TBI and the response to non-blinded, open-label treatment with anticonvulsant medications are concordant with the notion of neuronal inhibition, if noted in the absence of a clearly controlling mechanism of action. From a scientific viewpoint however, the treatment of fronto-limbic disinhibited patients has been neither blinded nor placebo-controlled to this point. As such, we can only provide an interesting observation of what appears to be a beneficial treatment response to anticonvulsant medication among patients with affective lability and AA/D following TBI. This indicates the need for a more systematic investigation of this phenomenon that, if substantiated, might improve the outcome and treatment choices for those patients who suffer from both TBI and AA/D. Further investigation requires us to focus on one agent for use in a soundly designed clinical trial. For this purpose, we have selected divalproex sodium.

Divalproex sodium is a standard and commonly used anticonvulsant and mood stabilizing agent that appears to be the best choice of active drug for the proposed study. It is a compound comprised of sodium valproate and valproic acid. In 1963, valproic acid was recognized to have anti-seizure activity, and it was approved as an anti-epileptic drug in the U.S. in 1978. The divalproex formulation, which is an enteric-coated, stable equimolar combination of sodium valproate and valproic acid, became available in 1983. In 1994, it was shown to be superior to placebo and comparable to lithium in treating acutely manic bipolar patients, and the FDA approved it in 1995 for this indication. Also, it is used in conjunction with lithium or carbamazepine to prevent recurrent manic or depressive episodes during long-term treatment of bipolar disorder (PDR, 2006).

This line of research opens an exciting area of inquiry that can 1) characterize a treatable clinical population more specifically than ever before and, 2) potentially offer an effective and widely available treatment modality that can ease the fronto-limbic disinhibition symptoms of TBI resulting in a significant lessening of ethanol intake for the same purpose. Because ethanol self-treatment often leads to increasing ethanol tolerance and the subsequent symptoms of AA/D, specific treatment for those suffering affective lability after TBI can potentially prevent AA/D in vulnerable individuals. In addition, specific treatment may also ameliorate AA/D in cases where it has already occurred. If found effective, anticonvulsant treatment for the mood and anxiety symptoms resulting from TBI offers the possibility of altering an otherwise downhill natural course into alcohol dependence, potentially affecting the many thousands of persons who suffer affective instability after closed head TBI. If proven, this treatment may act in both preventive and curative capacities. Last, establishing a treatment effect in this area will shed light on possible interactions between affective lability and neuro-inhibition as these relate to basic mechanisms whereby the brain's vulnerability to alcohol addiction becomes manifest. In short, if this study can demonstrate a valid effect it will open further doors of inquiry.

Body

As this was the first year of the study the primary task was to receive human use approval from all relevant institutional review boards and monitoring bodies. This process proved to be more arduous than originally anticipated. We submitted the study protocol for review with the Colorado Multiple Institutional Review Board (COMIRB) on September 26, 2008. Before we could proceed further, the board required that we seek an Investigational New Drug Application (IND) from the Food and Drug Administration (FDA) or a letter from the FDA documenting that this study did not require an IND. We submitted our IND Application on October 17, 2008. The FDA responded by granting us an exception from the IND regulations on October 27, 2008. This allowed our local review process to continue once more, and we were granted first COMIRB approval on November 12, 2008. Once COMIRB had approved the project we submitted for approval from the Department of Veterans Affairs Medical Center Research and Development Committee (VA R&D), who granted their approval on November 13, 2008.

We then submitted the project for review by U.S. Army Medical Research & Materiel Command (USAMRMC) Human Research Protection Office (HRPO). We received their Protocol Evaluation on January 30, 2009, including a list of items requiring completion and re-submission to both COMIRB and the VA.

At about this time the original study coordinator was replaced by Mr. Schmidt, who joined us in April, 2009, after an extensive recruitment. We revised the protocol in response to HRPO's stipulations in early May, 2009 and re-submitted the protocol to COMIRB. We received COMIRB re-approval on June 2, 2009. This was followed by VA R&D approval the following July in accordance with new regulations at that agency. Final HRPO approval was granted on July 17, 2009.

Shortly after this approval we received a Medication Safety Notice from the Department of Defense indicating that the study drug was among a class receiving a new black box warning from the FDA for risk of suicide. We responded to this notice by amending the study protocol to include a weekly measure of suicidal ideation. This protocol version was re-submitted to COMIRB for a third time, with approval granted on July 28, 2009.

On recommendation from COMIRB and VA R&D in late June we first consulted with and then on July 17 submitted an application for a Certificate of Confidentiality for the study to the National Institute on Alcohol Abuse & Alcoholism (NIAAA). We received comments from NIAAA July 30, 2009. With COMIRB recommendation for this certificate in mind, we nonetheless found that the NIAAA requirements conflicted with VA policies, specifically those regarding patient medical records conflicted with the protections afforded by the Certificate. Through further consultations with both Federal agencies, we could not reach a compromise between them. The process was deemed to be insoluble and we were unable to obtain a Certificate of Confidentiality for this study. This required us to submit another protocol amendment to remove the Certificate language from the consent form. COMIRB approved this amendment on September 1, 2009. VA R&D granted their final approval on September 15, 2009. We then submitted our COMIRB and VA R&D continuing review applications, which were approved on September 29, 2009 and will be in effect for the coming year.

In the initial Statement of Work we anticipated 8 months to achieve final approval for the study to begin recruiting the first entering subject. Owing to unanticipated complications the process actually took just under 12 months. These complications included FDA IND submission, personnel changes, alterations in the VA R&D submission and approval process, and determination that NIAAA/VA concerns with regard to the Certificate of Confidentiality

could not be negotiated. In the coming year we anticipate maintaining the current approvals as above and anticipate no personnel changes.

After receiving final approval from COMIRB, FDA, VA, and HRPO, as well as resolving the conflict between NIAAA and the VA, we immediately began outreach efforts to begin participant recruitment. Over the past month, Dr. Beresford and Mr. Schmidt have given outreach presentations to the Denver VA Medical Center (DVAMC) Substance Abuse Treatment Program (SATP), Mental Illness Research, Education and Clinical Centers (MIRECC), Inpatient Psychiatry, Outpatient Mental Health Clinic, TBI Clinic personnel and others.

The Research Pharmacy at the DVAMC has acquired, packaged, and recorded both the active drug and placebo preparations for this study.

At this time we have screened six potential participants in the past two weeks for enrollment into the study. At this rate we would screen 156 potential candidates yearly or about 13 per month. While it may not maintain this pace, we do, however, expect the rate of referral to increase dramatically as we continue to pursue active recruitment.

Key Research Accomplishments

At this stage of the investigation the study has not compiled any research data. Because of the nature of this investigation we do not anticipate accruing sufficient research data to describe accomplishments until the first review occurs after half of the subjects have been entered and finished the drug trial. We anticipate that occurring at approximately the 30th month of the study. This will entail data reported to the Data Safety Monitoring Board. Unless those data suggest an overwhelmingly positive or negative effect of the active drug, we anticipate principal research accomplishments based on data at the end of the drug trial.

Reportable Outcomes

Dr. Beresford presented an abstract, poster and oral presentation based on the preliminary study to the Military Health Research Forum held in Kansas City, MO, on August 31, 2009.

Conclusion

Any conclusions will occur after data collection and analysis.

References

01. Okie, S. Traumatic brain injury in the war zone. *New England Journal Medicine* 2005; 352:2043-2047.
02. Lishman, WA. The psychiatric sequelae of head injury: a review. *Psychological Medicine* 1973;3(3):304-18.
03. Nelson LD, Drebing C, Satz P, Uchiyama C. Personality change in head trauma: a validity study of the Neuropsychology Behavior and Affect Profile. *Archives of Clinical Neuropsychology* 1998;13(6):549-60.
04. Azouvi P, Jokic C, Attal N, Denys P, Markabi S, Bussel B. Carbamazepine in agitation and aggressive behaviour following severe closed-head injury: results of an open trial. *Brain Injury* 1999;13(10):797-804.
05. Bakchine S, Lacomblez L, Benoit N, Parisot D, Chain F, Lhermitte F. Manic-like state after bilateral orbitofrontal and right temporoparietal injury: efficacy of clonidine. *Neurology* 1989;39(6):777-81.
06. Perino C, Rago R, Cicolini A, Torta R, Monaco F. Mood and behavioural disorders following traumatic brain injury: clinical evaluation and pharmacological management. *Brain Injury* 2001;15(2):139-48.
07. Wroblewski BA, Joseph AB, Kupfer J, Kalliel K. Effectiveness of valproic acid on destructive and aggressive behaviours in patients with acquired brain injury. *Brain Injury* 1997;11(1):37-47.
08. Geraciotti TD, Jr. Valproic acid treatment of episodic explosiveness related to brain injury. *Journal of Clinical Psychiatry* 1994;55(9):416-7.
09. Pope HG, Jr., McElroy SL, Satlin A, Hudson JI, Keck PE, Jr., Kalish R. Head injury, bipolar disorder, and response to valproate. *Comprehensive Psychiatry* 1988;29(1):34-8.
10. Arciniegas DB, Silver JM. Regarding the search for a unified definition of mild traumatic brain injury. *Brain Injury* 2001;15(7):649-52.
11. Corrigan JD. Substance abuse as a mediating factor in outcome from traumatic brain injury. *Archives of Physical Medicine & Rehabilitation*. 1995;76(4):302-9.
12. Jorge R, Robinson RG. Mood disorders following traumatic brain injury. *NeuroRehabilitation* 2002;17(4):311-24.
13. Beresford TP, Arciniegas D, Clapp L, Martin B, Alfors J. Reduction of affective lability and alcohol use following traumatic brain injury: a clinical pilot study of anti-convulsant medications. *Brain Injury* 2005;19(4):309-13.
14. *Physicians' Desk Reference*. 60th ed. Montvale, NJ: Thomson PDR, 2006.
15. Beresford, TP. Reduction of affective lability and alcohol use following traumatic brain injury: a clinical pilot study of anticonvulsant medications. Military Health Research Forum, August 31, 2009, Kansas City, MO.

SYMPOSIUM S26-1, POSTER P20-1

REDUCTION OF AFFECTIVE LABILITY AND ALCOHOL USE FOLLOWING TRAUMATIC BRAIN INJURY: A CLINICAL PILOT STUDY OF ANTICONVULSANT MEDICATIONS**Thomas Beresford***VA Medical Center, Denver, CO*

Objective: A large and under-recognized subset of patients suffer both traumatic brain injury (TBI) and alcohol dependence (ADep). This group appears to use alcohol to self-treat affective and anxiety lability following TBI, resulting in new ADep, or worsened prior ADep. Our study hypothesized that treatment of such patients with mood-stabilizing medications would relieve post-TBI emotional dysregulation and facilitate reduction in alcohol use.

Design: We report retrospective medical record data from outpatients in our Substance Abuse Treatment Program who were treated for labile mood. Medications followed clinical indication and were given in non-blind fashion.

Method: Subjects included 18 patients who (1) complained of debilitating affective lability following TBI, (2) described drinking alcohol to ease lability symptoms, (3) met DSM-IV criteria for current ADep, and (4) were treated with a mood-stabilizing medication.

Results: During 6 weeks of treatment, 16 (89%) achieved abstinence from alcohol. All but two (14/16, or 88%) also showed improvement in their affective and anxiety symptoms.

Conclusions: These preliminary data are limited by the retrospective collection, clinical impression, and non-blinded trial. Nonetheless, the results suggest further investigation of anticonvulsants as potentially useful agents in comorbid emotional lability and ADep following TBI. Based on these observations, we have launched a double-blind, randomized, placebo-controlled trial that we expect to yield more definitive clinical results.

This work was supported by the U.S. Army Medical Research and Materiel Command under W81XWH-08-2-0652 and Department of Veterans Affairs.