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

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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. Active subject recruitment continues. There are no results to report at this time.					
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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 self-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

Recruitment

This report closes the fourth year of study funding. As it took substantial time locally to receive all approvals for this project, we began enrollment near the end of the first year. For our initial efforts we targeted services and clinics at the Denver VA Medical Center (DVAMC) who regularly saw TBI patients. Dr. Beresford and Mr. Schmidt continue to provide outreach presentations to the Substance Abuse Treatment Program (SATP), Mental Illness Research, Education and Clinical Center (MIRECC), Inpatient Psychiatry, Outpatient Mental Health Clinic, TBI Clinic personnel and others. We also have continued generalized outreach, advertising the study throughout the DVAMC with flyers and brochures. We consented our first participant in October 2009. This was followed by the first subject to be randomized to the study drug trial in February 2010. Since then we have expanded our outreach beyond the DVAMC by running advertisements in two local newspapers and made contact with Operation TBI Freedom, a local organization dedicated to working with Veteran TBI patients. Our best sources of subject referrals have been 1) flyers in the VA facility and in selected community sites such as local colleges that work with returning veterans, and 2) community advertising in weekly newspaper venues.

We continue to screen patients and enroll at a steady pace. As of October 1st, 2012, we have randomized 32 patients into the drug trial (Figure 1) from a population of 270 potential candidates, of whom 63 were evaluated for study entry in person. We have collected usable data from all 32 subjects randomized and a total of 23 (71%) have completed the protocol. As this number is below the recruitment goal of the study, in July we requested and were granted a no-cost extension of one year to the original timeframe of the study.

Projecting our fourth year enrollment rates (Figure 2), however, we recognize that the present pace will not result in timely completion of the study. This caused us to review the enrollment experience of the past seven months, March through September, 2012, as compared to the same period in 2011, recalling that we opened study to non-veteran subjects in December, 2011. As in the Table below, while our phone screen frequency nearly doubled (+89%), both the % consented and the % randomized dropped significantly over the same period.

Subject Recruitment Experience, 2011 vs. 2012			
	March-September, 2011	March-September, 2012	Change
% consented	32.6	10.3	- 68%
% randomized	10.9	2.3	- 79%
2011 to 2012 Calls (n)	46	87	+ 89%

This strongly suggested that including non-veterans alone did not assist in increasing our recruitment productivity despite our best efforts in both community outreach and concurrent recruitment from within the VA community. While the number of study inquiries received increase dramatically, two factors appear to account for this difficulty: 1) the non-Veteran participants have sustained more serious brain injuries, and 2) the non-Veteran participants do not have other medical care available to them (i.e., they are uninsured). These two factors create situations in which non-Veteran participants received little or no follow-up care following acute

recovery from their injury and arrive in the study with higher co-morbidity. This has required careful assessment and necessitated excluding otherwise appropriate candidates.

In the past year we have also explored new methods of outreach, including advertising in local public transportation. While this effort was successful in increasing the number of telephone inquiries we received, the number of subjects who enrolled in the study through this method of advertising was also disappointingly low. In the coming year we will continue to explore alternative media venues for promoting the study. We are currently developing an additional television advertisement that we anticipate will increase our exposure. We will also be developing a similar radio advertisement in order to more effectively reach potential participants.

In the coming year we also plan to hire additional dedicated staff to promote the study and continue our outreach efforts primarily targeting the Veteran population. Having additional personnel will allow us to increase our presence in clinics that treat our target population as well as devote more time to in-person interactions.

Reviewing our randomized subjects to this point, we are pleased that participant compliance continues to be remarkably high, with 71% (23/32) completing the protocol once randomized, well above the anticipated 50% dropout rate.

Pilot Investigations

In working with this group of patients we have noticed several patterns emerging that offer new avenues of potential investigation.

1) Do alcohol and TBI contribute independently to brain sub-structure volume changes?

We have now acquired MRI scan data on 32 subjects, a sufficient sample size to begin automated volumetric analysis. In the coming year, we will follow this year's quality review of scans with Dr. Davatzikos and compare the study scans against MRI data from both a) a pre-existing group of alcoholics with no history of TBI as well as b) a normal non-alcoholic, non-TBI control group. These groups will be matched for age and gender, and will allow us to investigate the extent to which head injury affects the structural changes that occur in the brain over and above those expected from alcohol abuse. Brain volume comparisons will be made, including automated measures of brain sub-structure volumes (Beresford et al, 2006).

2) Cognitive Impairment in Individuals with Co-Morbid TBI and Alcohol Abuse

We examined frontal cortical functioning using two measures from the current study. Last year we observed that the Frontal Assessment Battery (FAB) revealed that 41% of subjects (12 participants) scored greater than 2 standard deviations below the normal adult mean, indicating frontal dysfunction in those persons. At the same time, the Trail Making Test, Part B (TMT-B), identified 66% of subjects (19 participants) as outside 2 standard deviations of the normal adult mean, indicating specific frontal executive function deficit. We reported this finding at the June, 2011, annual scientific meeting of the Research Society on Alcoholism and are pursuing this aspect of the study further as the sample size increases.

3) Can we separate components of PTSD and TBI in this population?

Because we previously noticed a large number of our participants report Post-traumatic Stress Disorder (PTSD) symptoms, we studied a separate sample (n=115) of Denver veterans treated for PTSD with and without histories of TBI, with results as follows. 1) Compared to patients with no history of TBI, those with one or more TBIs showed less improvement in PTSD symptoms through PTSD treatment, as assessed by the Mississippi PTSD scale (M-PTSD). 2) Veterans with a history of alcohol abuse may evidence improvement in PTSD symptoms even if

they also have a history of TBI. 3) Clinically, patients who stop abusing alcohol prior to PTSD treatment may improve more quickly and make greater gains as they heal from alcohol exposure. 4) By contrast, patients with TBI alone appear to make little gain on the M-PTSD, consistent with TBI recovery, which is thought to reach its maximum within one year after injury. 5) Contradictory results on two PTSD scales (M-PTSD and the Post-Traumatic Disorder Checklist – Military Version or PCL-M) suggest that some PTSD scale items may reflect TBI rather than PTSD, echoing concerns in the literature on differentiating the two. We concluded that further research is warranted to illuminate the differential effects of alcohol and/or TBI on PTSD treatment and recovery. This work was also presented at the June, 2011, annual scientific meeting of the Research Society on Alcoholism. This is the topic was positively reviewed as a CDMRP pre-proposal but did not reach funding score level in the early 2012 round of CDMRP research project competition although the scores were generally favorable and the critiques very useful in proceeding to a new submission of this project idea as opportunity occurs.

Key Research Accomplishments

At this stage of the investigation the study continues to compile and store research data. According to study design we have not yet begun to analyze these data with respect to the study hypotheses. After reaching the 50% of recruitment, we completed a blinded, mid-course data quality review during the past year. Those data did not suggest an overwhelmingly positive or negative effect of the active drug, and indicated the need for accruing the original sample size. We anticipate elucidating principal research accomplishments once enrollment is complete, the study blind is broken and we analyze the data.

Reportable Outcomes

None at this time.

Conclusion

Any primary conclusions from the blinded study will occur after data collection and analysis have been completed and the study blind opened at that point. In the meantime we will continue to formulate and explore new questions and hypotheses from non-blinded data.

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Appendix

Figure 1:

Enrollment Log

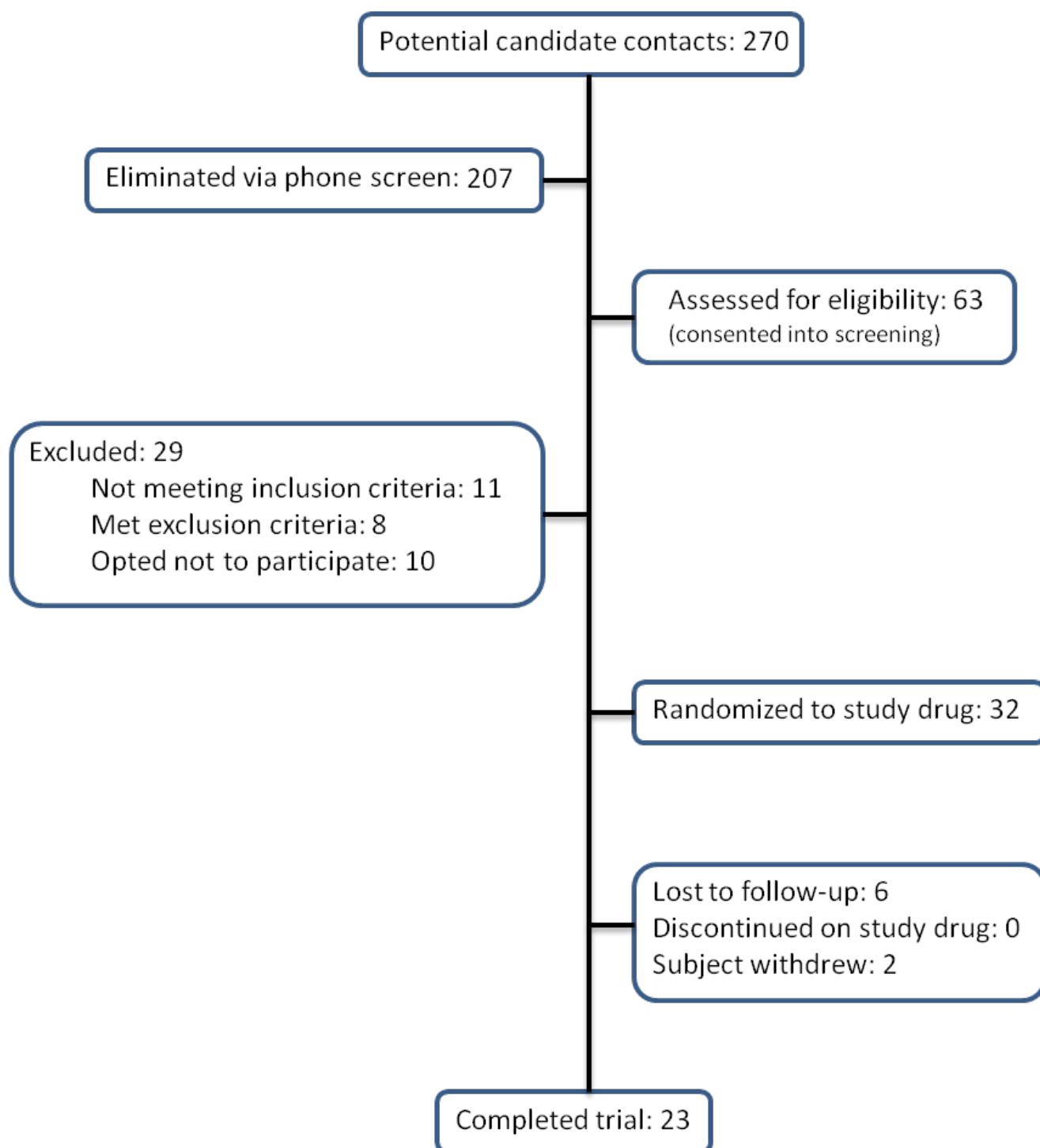


Figure 2:
Participants Randomized

Exposure to Drug

