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TITLE: Preventing Epilepsy after Traumatic Brain Injury

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14. ABSTRACT The purpose of this study was to determine the feasibility of performing a single center epilepsy prevention trial after traumatic brain injury (TBI), to determine safety and tolerability of topiramate in the treatment of early seizures following TBI, and to compare the efficacy of topiramate to prevent early seizures to the standard of care (phenytoin). A secondary objective was to obtain data necessary to design of a randomized clinical trial for preventing epilepsy and improving neurological outcome after TBI. Initially, we formulated the protocol and documents required by regulatory bodies and received approval by the IRB at the University of Pennsylvania, HRRPO at the USArmy, and the FDA. The infrastructure for the study was established, including interactions with the trauma center, neurosurgical services, EEG laboratory, pharmacy, etc. Subject recruitment began but was initially very slow and the protocol was revised to eliminate several major obstacles. Ultimately, we enrolled many fewer subjects into the study then intended and the reasons for that were carefully analyzed, as were other lessons learned from the pilot trial. We have also organized a NINDS workshop on Biomarkers for Epileptogenesis and a program to assist gulf war veterans with TBI, and have been influential in enhancing epilepsy care for veterans within the DVA.

15. SUBJECT TERMS

None listed.

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Table of Contents

INTRODUCTION:

The purpose of this study was to determine the safety and tolerability of topiramate (Topamax®) in the treatment of early seizures following traumatic brain injury (TBI), to determine if topiramate could prevent early seizures better than the current standard of care (phenytoin) and to develop a methodology for conducting a multicenter randomized clinical trial for the prevention of epilepsy and improvement of neurological outcome after TBI. We initially hoped to enroll approximately 90 patients at the University of Pennsylvania in the pilot study. Patients with moderate to severe head trauma who met entry criteria were to be randomized to one of three arms of the study. One arm would receive topiramate for seven days, the second arm would receive topiramate for three months, and the third, control, arm would receive phenytoin for seven days (current standard of care). EEGs were to be performed continuously for seven days from onset of the study (within 24 hours of TBI) to look for early, non-clinical, seizures and for electrophysiological biomarkers for the process of epileptogenesis. The patients were to be monitored for clinical seizures, subclinical, electrographic seizures, and recovery of function. Patients were also to have MRI scans at one month and twelve months to assess structural damage to the brain. Patients were to be followed for two years to determine if epilepsy subsequently developed and to assess level of functional recovery.

BODY: The original Statement of Work indicated four sets of projects to be accomplished during the grant period. We have completed these objectives.

In the first year of the study, we formulated the protocol for the clinical trial, created case report forms and case books, and developed the informed consent documents and other documents required by regulatory bodies. All of these were submitted to the IRB at the University of Pennsylvania, the US Army, HRPO, and the FDA. The approval process for this protocol, especially from the HRPO, took approximately one year. During this time we established the infrastructure for the study, hired relevant personnel and organized the patient recruitment methods, interactions with the trauma center, neurosurgical services, EEG laboratory, pharmacy, etc. in order to conduct the research. Once all the regulatory and infrastructural issues were accomplished, we began attempting to recruit subjects for the study.

Below we present the original SOWs (in italics) and our accomplishments during the course of the research:

SOW - Task 1: *Develop instruments for a pilot (and subsequently, full) clinical trial for epilepsy prevention after head injury.* This has been accomplished by the development of the clinical trial protocol, informed consent, case books, and regulatory documents. All of these have received approvals by the University of Pennsylvania IRB, the USArmy HRPO, and the FDA. This approval process took approximately one year to complete. The most prolonged component was the HRPO.

a. Develop the web-based clinical trial instrument now being tested at the University of Pennsylvania for use in clinical trial for epilepsy prevention after head injury. (This study management tool will act as the primary system for managing all aspects of the clinical trial, including functioning as a central repository of all research studies and associated personnel, budget set-up and financial tracking, self-population of standard forms, tracking of IRB and other regulatory approvals, subject scheduling and processing, and overall study tracking. It is expected that once this instrument is fully implemented for this neuroprotection study, it will be easily reformulated for other neuroprotection trials.) We have accomplished this task utilizing web based tools generated by the Office of Human Research at the University of Pennsylvania, but did not formally adopt the web-based clinical trial instrument. Instead,

we developed these tools internally. We investigated several software packages designed specifically for use in clinical trials of various sizes, that would be suitably powerful, but also suitably "user friendly" to permit study personnel to enter data efficiently and also permit continuous data monitoring and evaluation. We purchased licenses for the Science Trax Software package (Study Trax). This software is especially designed for use in research. Users can easily learn and adopt the application. The analytical process is streamlined because the user has the ability to create analysis-ready data sets that export to statistical packages. This eliminates the dependency on technical staff to create and export data and it also reduces the burden on the staff by allowing the subjects to enter data via the internet. Because of the limited subject enrollment in the protocol, we did not fully implement this analysis package.

b. *Develop web-based clinical data base for use in epilepsy prevention trial.* We chose to use a simpler, more easily available data base for the early pilot program, as the expense for developing a more comprehensive web-based data base was beyond our budgetary capacity.

c. *Develop brain image data base (BRAID) that can be combined with the clinical data base for use in epilepsy prevention trial.* We have established appropriate MRI protocols for the TBI study in collaboration with the neuroradiology group at the University of Pennsylvania to permit collection of MRI data on the TBI patients in the study and incorporate these images into a BRAID data base being developed at the University.

d. *Combine instruments developed in above into a specific clinical protocol for a 3 arm study designed to prevent epilepsy after moderate to severe head injury.* This has been accomplished and has passed all regulatory requirements.

SOW - Task 2: *Develop the infrastructure for implementation of randomized double blind trial to prevent epilepsy after head injury.* This has been accomplished.

a. *Establish procedures with trauma team and ER personnel for identifying candidates for epilepsy prevention trial.* We initially mobilized collaborators in the ER, the Trauma Unit, and the Neurological/ Neurosurgical Intensive Care Unit to participate in the study. We held meetings with the teams to provide in-service training. As we began implementing the study, it became apparent, for a variety of technical reasons, that we would be unable to recruit patients into the study within the original 12 hour window that we specified, and that we would not be able to start the topiramate before many of the patients received a phenytoin load (standard of care that did not require informed consent by the patient or a legally authorized surrogate.) We then changed the protocol to increase the entry window to 24 hours and to have every subject receive a loading dose of phenytoin before being randomized to up to 6 days of topiramate or 3 months of topiramate. This allowed us to begin successfully recruiting subjects. Despite these changes, however, recruitment continued at a slow pace. Reanalysis of the patients entering HUP with traumatic brain injury indicated that a significant number arrived outside the 24 hour window, often after stabilization at outside hospitals. Other subjects who did arrive at the hospital within the 24 hour window did not have identifiable and available family contacts to provide informed consent in person, which we were required to obtain before entering anyone into the study. After multiple attempts to enter subjects in a timely fashion, we modified the protocol to open the window of eligibility to 72 hours and have obtained regulatory approval from the Penn IRB, FDA, and HRPO. Details of our subject identification and recruitment methods are provided below.

b. Establish procedures to obtain appropriate consent from subjects that are too impaired to provide conventional informed consent. This would involve obtaining consent from individuals who are legally identified as being able to provide consent or by obtaining community consent. This has been accomplished to the satisfaction of all regulatory bodies involved. This is not a trivial issue, since most of the subjects arrived to the ER in a state that prevented them from being able to provide informed consent (e.g. either comatose or mentally impaired). As mentioned above, our initial protocol required administration of the first dose of antiseizure drug by 12 hours from the TBI, so we needed to reach the appropriate, legally sanctioned individual associated with each subject to provide informed consent. We were not permitted to utilize either waiver of consent, or "community consent" under current HRPO guidelines, and we were not permitted to obtain informed consent over the telephone, even temporarily. Thus, we had to rely on being able to communicate directly and in person with appropriate legally authorized surrogates within 12 hours of the TBI. This required that our study personnel be available 7 days per week, 24 hours per day. As mentioned above, it turned out to be virtually impossible to identify candidates for the study and identify appropriate individuals for obtaining informed consent in person, within the guidelines initially established, as especially as individuals with TBI often presented late at night, on weekends, and with appropriate "consenters' unavailable. As discussed above, for this and other reasons, the protocol has been revised twice.

c. *Develop and promulgate standardized treatment protocol for head injured patients.* This was accomplished in collaboration with our neurosurgical team.

d. *Establish pharmacy program for administration of study medications in a double blind manner.* This was accomplished with the HUP Interventional Drug Services (IDS).

e. Establish procedures for obtaining continuous EEG monitoring for up to 7 days post head injury. This was accomplished by recruiting talented EEG technologists to perform and monitor these tests and be dedicated to this protocol. These technologists already had experience performing continuous EEGs on TBI patients from a preliminary study (without drug intervention) that we had begun at the University of Pennsylvania. In addition, we developed the techniques to use EEG electrodes that were CT and MRI compatible so they would not need to be removed each time a patient with TBI required an emergency study as part of their clinical care. These electrodes are part of the standard care for patients in the Neurological Intensive Care Unit who are on continuous EEG monitoring.

f. *Establish internal and external data and patient safety monitoring boards.* We have engaged an outside clinical trials auditing group to periodically audit our clinical trial and make sure that there are no serious deviations from our protocol. We established an internal safety review process by having a separate faculty member, who was not otherwise involved in the study but has experience with critically ill patients, serve as a study safety monitor. We initially intended to establish an external Data Saftey Monitoring Board, but our low enrollment made it unnecessary. (An external DSMB is not required by the regulatory bodies, but it would have been useful for the study if we had achieved a much larger enrollment and experienced any adverse events in the subjects, even if they were deemed unrelated to the study medication or procedures.)

SOW - Task 3: *Implement pilot clinical trial to prevent the development of epilepsy in individuals with moderate to severe head injury by 7 day and 3 month treatment with topiramate*

a. After receiving approval from all the relevant regulatory agencies, we began to screen TBI patients arriving in the trauma unit of the Hospital of the University of Pennsylvania for entry into the study. At this point we encountered two major and unexpected problems. First, because of our inability to enter

subjects into the study based on either a waiver of informed consent or community consent, we needed to have a personal interaction with the legally designated representative of the patient with TBI in order to obtain informed consent to enter them into the study. Because moderate to severe TBI often results in impaired consciousness, judgment and cognitive function, we most often were unable to obtain informed consent from the subjects, themselves. Obtaining proper informed consent from surrogates proved to be exceedingly difficult within the original 12 hour window for admission that was initially established. Secondly, although before the study had begun, we analyzed initial treatment of TBI patients at HUP and determined that many, for a variety of legitimate reasons, did not receive phenytoin within the first 12 hours, once the study commenced and administration of an antiepileptic drug became part of the protocol for all patients with moderate to severe TBI, it was impossible to withhold phenytoin for the12 hours during which informed consent, randomization, medication distribution, etc was occurring in the protocol. Third, a significant number of patients arrived at HUP close to, or just after, the 12 hour window, so they could not be recruited for the clinical trial.

b. After screening more than 100 patients over the first 6 months after the protocol was approved, we determined that the pilot program would need to be modified in order to accomplish its goals. Accordingly, we submitted a revised protocol to the IRB at the University of Pennsylvania, the FDA and the USArmy HRPO. The revised protocol allowed all subjects to receive a loading dose of phenytoin within 3 hours of being admitted to the trauma unit (standard of care), allowed for a 24 hour window for admission to the study, and lowered the initial loading dose of topiramate. The remaining elements of the pilot trial remained as they were. At that point, we hoped that these changes would permit recruitment to proceed.

c. Although the revised protocol did permit successful recruitment of subjects into the study, this continued to be an unacceptably slow process. This was surprising as our preliminary studies indicated that we would be able to accrue many more subjects then we subsequently did. One possible explanation, as discussed in local newspapers, is that the “fire power” of guns in the streets of Philadelphia has increased over the last few years, so it is possible that individuals who had gunshot wounds to the head were now much more seriously injured (often fatally) and this cohort of potential subjects was much less available then in prior years. Furthermore, we lost a significant number of possible candidates because they had a history of drug addiction or had illicit drugs found during routine admission toxicology screens or were involved in a police matter. In addition, when we analyzed our recruitment data, we realized that significant numbers of patients were reaching Penn outside the 24 hour window, often because they were first seen at outlying hospitals and were then transferred to The Hospital of the University of Pennsylvania (HUP) after some medical stabilization. Consequently, we revised our protocol to allow a 72 hour window after TBI. This was submitted to the Penn IRB, FDA, and HRPO, and was been approved by all of the regulatory agencies.

SOW 4: *Interim data analysis*

Our limited patient enrollment in this pilot clinical trial severely restricted the data analysis from the trial. All subjects were monitored throughout their hospital care at the Hospital of the University of Pennsylvania.

Attempts were made to maintain follow up contacts with all subjects but that became more problematical. (Evaluating the ability to maintain follow up with the subjects was one of the objectives of the pilot study.) One subject, a young woman shot in the head, possibly accidentally at a party, was involved in the ongoing criminal investigation of the shooting and declined to cooperate after being discharged from the hospital. She had recovered function from her injury and at last contact

had not had any seizures. Another subject was an immigrant from West Africa who as involved in a MVA. After recovering in the hospital, she returned to her home in Africa and could not be reached. A third subject moved out of the area after discharge. A fourth subject developed breast cancer shortly after discharge and decided to withdraw from follow up in order to attend to her other, more pressing, illness. Each of these was totally unexpected, but if plans go forward with a more definitive multi-center study of epilepsy prevention after TBI, will need to be considered when formulating the protocol.

Once subjects were enrolled, we were able to obtain long term EEGs, but with frequent interruptions as patients went for imaging studies or additional surgical procedures. We collected sufficient data to analyze for subclinical seizures and possibly for some biomarkers, however. In fact, we did not record early subclinical or clinical seizures in any of the subjects that were admitted to the study. In the subjects that were available for follow up, we were able to obtain EEGs at 3, 6 and 12 months post TBI. We were also able to clinically evaluate the patients for recovery of function and obtain seizure questionnaires. We did not have enough patients enrolled to determine if topiramate was as good as, or better than, phenytoin in preventing early seizures after TBI. It did appear safe and well tolerated in this small sample, as expected for a moderate dose of a commonly used antiepileptic drug.

DETAILS OF SCREENING:

The main problem encountered in our attempt at a single center pilot clinical trial was the very limited number of subjects that could be successfully recruited into the study. We monitored and analyzed the recruitment methods repeatedly throughout the study to try to increase our enrollment. This initially led to two protocol revisions, each of which incurred significant delays because of the necessity of obtaining approvals from three different regulatory bodies, one after the other. We initially screened subjects by having someone dedicated to identifying subjects in the ER/Trauma Bay 24 hours per day, 7 days per week. This was possible because of a program established by one of our co-investigators to recruit subjects into any of several clinical trials that began with ER visits. In addition, each morning, the study coordinator reviewed all ER/Trauma admissions and all head CT scans performed in our Emergency Department to identify subjects who had been seen overnight and whose CT scans indicated lesions that were part of our inclusion criteria. (All patients with moderate or severe TBI seen in the HUP ER have CT scans as part of their evaluation. The CT scanner is adjacent to the ER and is used exclusively for ER patients.)

As mentioned above, even when specific subjects were identified by this method, it was impossible to obtain appropriate informed consent within initially the 12 hour post TBI window, and later, even within a 24 hour window. In addition, early in the study, many of the patients received phenytoin quickly, as part of standard of care, and so were not eligible for our study. In the 12 month period between May 2006 and April 2007, 158 eligible subjects with TBI were identified in the ER or Trauma Bay. Of those individuals, 6 were too severe for our protocol, 70 were seen outside the 12 hour window, 8 had an indeterminate time of injury, 32 had no available family for consent, and 21 were given phenytoin before they could be randomized. An additional 21 subjects had other exclusions, most often illicit drugs were found in toxic screens. No patient who was otherwise eligible refused to enroll in the study. From May 2007 through Dec 2008, when enrollment was stopped, another 100 subjects with TBI were identified through our screening procedures. Among these, 37 were seen outside the post-TBI time limits, 3 were too injured for the study, 9 had an indeterminate injury time, 25 had no available family for informed consent, and 24 had other exclusionary criteria, again, most often for illicit drug use. One eligible patient refused the study – an adult daughter said her mother

"would not want to be a guinea pig in an experiment", even though she was only being asked to participate in EEG recording and randomization to one or another antiepileptic drug. Ironically, since continuous EEG recording is being used as standard care in our neurological ICUs and antiseizure drugs other than phenytoin are being employed as well, the patient's clinical course was likely very similar whether she was in the study or not, and her follow up would certainly have been better had she been a study participant. Fortunately, only one subject during the entire period of clinical accrual refused consent.

LESSONS LEARNED FROM THE PILOT CLINICAL TRAIL:

1. A single center trial for TBI is very difficult, despite what appeared to be an adequate patient population
2. The nature of the patient population very important
3. A decision must be made before the protocol is developed about how to deal with subjects that use illicit drugs and/or alcohol
4. It is very important to obtain either community consent or waiver of consent in order to enroll subjects into the study early. This should be relatively straight forward for a drug or intervention that is standard (such as an already approved antiepileptic drug). If the study is funded by a source that does not permit community consent as a regulation, or in a jurisdiction that does not recognized community consent, it will make the study much more difficult.
5. The initial entry time window should not be too short unless there is compelling data that the treatment needs to be immediately initiated.
6. There is a need to distinguish "normal" clinical care, such as continuous EEGs, from the "experimental" procedures.
7. There cannot be "rescue" trial ongoing with the patient population, as that would preclude adding a second clinical trial to prevent epilepsy.
8. It would be best if the trial is run via a department that sees the patients first, or by a very closely integrated team, to avoid "communication" issues with hospital personnel who first interact with the patients.
9. Obtaining continuous EEGs is possible but needs focused attention and support and supporting a dedicated EEG technologist adds significantly to the cost of the trail.
10. The addition of significant amounts of testing to ensure no disruption of recovery of function after TBI makes the trial costly
11. It is necessary to decide on an early treatment – PHT or drug under study. Since PHT administration within as short a time as possible is considered standard of care for TBI, it is likely that all patients must receive this before being randomized to any experimental treatment, unless the experimental drug is an AED that may be equally or more effective than PHT in suppressing early clinical seizures. If the experimental treatment is not an AED, it is likely that all subjects may need to start on 1 week of PHT.
12. Follow up of patients may be complex for reasons that are entirely independent of the trial and the TBI experienced by the patients.

KEY RESEARCH ACCOMPLISHMENTS:

- Write clinical protocol
- Develop informed consents
- Develop case report forms
- Explore various software packages designed for developing clinical trial data bases
- Submit documents to University of Pennsylvania IRB and obtain approval
- Submit documents to US Army HRPO and obtain approval
- Submit documents to FDA and obtain IND
- Recruit EEG technologist
- Arrange for randomized drug distribution with Pharmacy
- Arrange collaborative efforts with emergency room, neurosurgery and trauma units
- Establish mechanism for rapid identification of subjects upon arrival in trauma unit
- Develop in-service training for relevant personnel
- Establish brain imaging protocols
- Revise protocol, informed consent and case report forms twice, based on initial unsuccessful recruitment period
- Recruit 6 patients into the study
- Obtain follow up EEGs and MRIs on some, but not all, subjects enrolled in the study
- Organize and lead an NINDS sponsored workshop on Biomarkers for Epileptogenesis
- Identify electrophysiological, imaging, biochemical and genomic biomarkers that might be useful in monitoring the process of epileptogenesis and the response to potential therapies
- Detailed analysis of recruitment difficulties and other major logistical issues in any trial designed to prevent epilepsy after TBI

REPORTABLE OUTCOMES: To date, there are no reportable outcomes with regard to the specifics of the pilot clinical trial. The results of the Biomarkers for Epileptogenesis workshop were presented in March, 2007 at the 9th bi-annual Antiepileptic Drug Trials meeting held in Florida. Several of the conclusions from this workshop were incorporated as NINDS guidelines in the Curing Epilepsy Conference that was held in Bethesda, MD in March 2007. Dr. Dichter delivered an invited lecture at the Merritt-Putnam Symposium during the Annual Meeting of the American Epilepsy Society that focused on translation of basic science discoveries into therapies to prevent epilepsy. This lecture highlighted issues related to clinical trials in anti-epileptogenesis and emphasized how little clinical research is being performed in this area throughout the US and the world. This lecture was published in Epilepsia (Ref 4, below).

Dr. Dichter was also chosen to give the Soriano Lecture at the American Neurological Society's Annual Meeting and discussed emerging concepts in the pathophysiology of epilepsy and epileptogenesis. This talk focused on the need to develop translational programs in antiepileptogenesis, even while neurologists await more basic information about how best to prevent epilepsy after risks such as traumatic brain injury. This lecture was converted into a manuscript and published in the Archives of Neurology (Ref. 5, below).

Dr. Dichter is also developing a website that would focus on risk factors for developing epilepsy, a syndrome he calls the RED syndrome. Collaborating with epilepsy specialists and epidemiologists from all over the world, this web site will allow clinicians and patients with various risks, such as TBI, brain tumors, intracerebral hemorrhages, prolonged febrile seizures, etc to estimate the risk of developing epilepsy over a defined time period and then will discuss how this risk assessment was

determined, including a source of references. When the information becomes available, methods for lowering the risk will also be discussed.

CONCLUSIONS: This grant was designed as a pilot clinical trial to test feasibility and safety of a program to prevent epilepsy after TBI. Many of the objectives of the grant were successfully concluded, despite a low enrollment in the trial itself. This is especially important as there was only one similar trial to this ever accomplished in the US (at the University of Washington), and the current trial design had some significant enhancements over that trial design. In the first year, we successfully completed all the pretrial components and received all the necessary regulatory approvals. This included a preliminary feasibility trial where we performed up to 7 days of continuous EEGs on TBI patients who were not part of this research protocol and who did not receive any specific antiepileptogenic seizure intervention beyond current standard of care. Developing the infrastructure for this kind of trial and successfully navigating all the potential issues in an acute intervention trial in severely injured patients was not a trivial task. Similarly, coordinating multiple medical teams, each of which is focused on their own tasks with regard to major trauma cases (e.g. trauma surgeons, neurosurgeons, emergency room personnel, nurses, pharmacy, etc.) was also a significant accomplishment. By the middle of the second year we began recruiting subjects. After screening more than 100 TBI patients in our trauma unit over six months, we realized that there were major procedural obstacles to completing the pilot trial as originally formulated (see SOW - Task 3, above) and we modified the protocol twice to circumvent these problems without compromising the study. We continued to screen all eligible patients appearing at HUP. However, it became clear that the recruitment continued to be very slow. We have summarized our recruitment strategies above, and have also indicated a series of important methodological outcomes ascertained from this pilot trial in the section on “Lessons learned…” We consider these two sections as critical “successes” of the trial, as they will serve to make any additional efforts in this area much more likely to be successful. One overarching lesson that one can take away from this pilot trial is that the proper conduct of a clinical trial may be as difficult as the discovery of a drug or treatment that might prevent epilepsy after TBI. Neither arm of this research program can be neglected or postponed. A “cure” without a means of properly and efficiently demonstrating such in human subjects will not be worth much. A poorly designed and inadequately accomplished clinical trial could even set back the development of a potentially valuable treatment. Obviously, a well done clinical trial with an ineffective agent will also not solve the problem.

In addition to the direct pilot study in preventing epilepsy after TBI, we have a achieved a significant accomplishment with regard to a very important issue related to this study and one which was not submitted as a major part of this grant. We initiated a program in conjunction with the National Institutes of Neurological Diseases and Stroke to hold a conference on Biomarkers of Epilepto-genesis. Our reasoning was that we were developing a unique resource for trying to study this issue in humans as an adjunct to our study and with no additional risk to our patients. We are collaborating with the only two groups in the US who have been, or are currently, engaged in epilepsy prevention trials – The University of Washington (who recently completed their third, unfortunately negative, clinical trial to prevent epilepsy after TBI) and a group in Washington, DC launching a small pilot trial of preventing epilepsy after TBI (although with less severely injured patients than we are studying and without continuous EEG recordings). This conference brought together researchers at both the clinical level and animal model level to consider what is known about the process of epileptogenesis and how we might develop biomarkers of the process using electrophysiology (including highly sophisticated signal processing techniques that are not standard in this field), imaging, biochemical markers in CSF and serum, and genomics. The results of this conference have been presented at an

international meeting on new antiepileptic drugs and at lectures at the annual meeting of the American Epilepsy Society.

A related accomplishment, also not directly part of the original grant, but something that was inspired and stimulated by the clinical trial being sponsored by the US Army, was the establishment of Operation Giveback by Dr. Dichter and the American Epilepsy Society. As more and more information was being released about the extent of TBI in the returning veterans of the gulf wars, Dr. Dichter became increasingly concerned about the possibility that many of these injured veterans would be susceptible to developing posttraumatic epilepsy, months or even years after returning to the US. Some of these seizures might not be recognized as seizures, if they remained partial and did not generalize. Thus, these veterans might be assumed to be suffering from continued cognitive or behavioral disorders when, in fact, they may have been experiencing treatable seizures. Dr. Dichter developed a program, called “Operation Giveback” to galvanize the epilepsy community to try to make sure none of these veterans “fell through the cracks” of optimal medical diagnosis and care for their possible post-TBI epilepsy. He proposed this plan to the AES, as well as to other national neurology organizations, and it was adopted by the AES, and enthusiastically endorsed by the other organizations. A task force was formed to determine where the needs were and how AES members could assist the DOD and DVA, as well as working in the private sector, to facilitate care for the possible posttraumatic epilepsy that might develop in the wounded veterans. Educational programs were developed to try to reach the veterans, their families, and primary care providers, to make everyone aware of this problem, especially the subtleties of the seizure presentations (see AES website).

A third accomplishment, also not part of the original proposal but occurring in the context of increased interest in preventing epilepsy after TBI relates to enhanced efforts within the Department of Veterans Affairs for returning veterans who experienced TBI and might develop posttraumatic epilepsy. Dr. Dichter and other epilepsy specialists in the AES worked to support congressional legislation to expand epilepsy services with the DVA by establishing four new Centers of Excellence throughout the country that would enhance and expand services available to veterans with regard to epilepsy diagnosis and treatment. This legislation was passed and Dr. Dichter was asked to serve on the small panel that reviewed the grant submissions for the DVA. The four CoEs were chosen and the awards have now been made. Dr. Dichter was then asked to direct a small panel to oversee implementation of the grants, to monitor progress in epilepsy care among veterans, especially veterans of the gulf wars, and to promote integration of the programs across a national level.

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APPENDICES: N/A

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