



Post-traumatic Epilepsy: research at the VA

Robert L Ruff, MD, PhD
National Director for Neurology
Veterans Health Administration

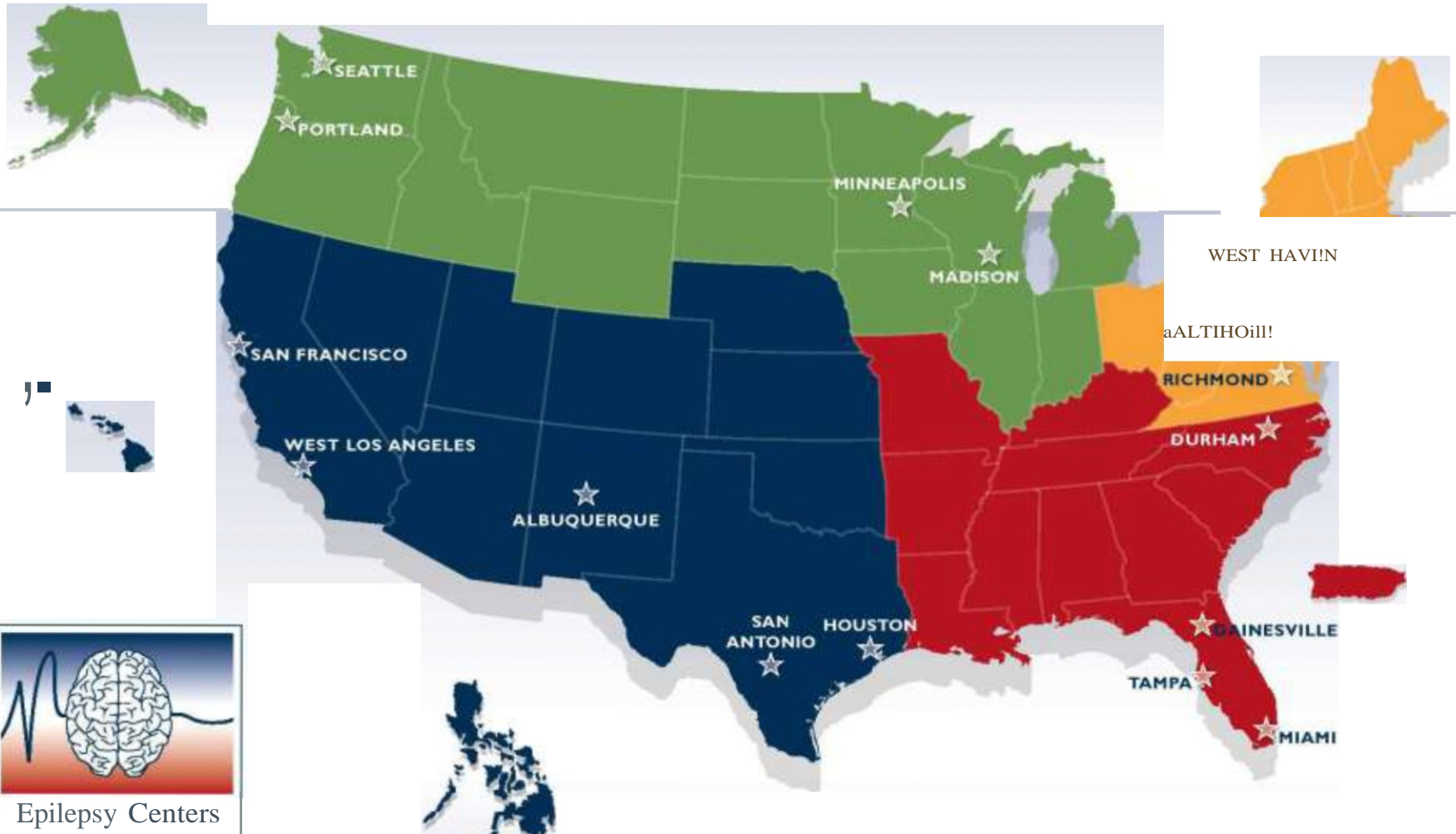
Interagency Collaborative to Advance Research In
Epilepsy (ICARE)

Establishment of Epilepsy Centers of Excellence (ECoE)

- Public Law 110-387: Veterans Mental Health and Other Care Improvements Act of 2008
- Centers must:
 - link to existing VHA Polytrauma Centers
 - link to academic centers and conduct research
 - be established by a Peer Review Panel
 - be involved with education and fellowship training
 - develop veterans epilepsy databases
- Funding Cycle October 2008-September 2013

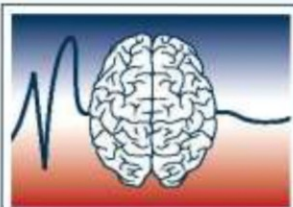
EPILEPSY CENTERS OF EXCELLENCE REGIONAL MAP

DEPARTMENT OF VETERAN AFFAIRS



WEST HAVIN

aALTIHOill!



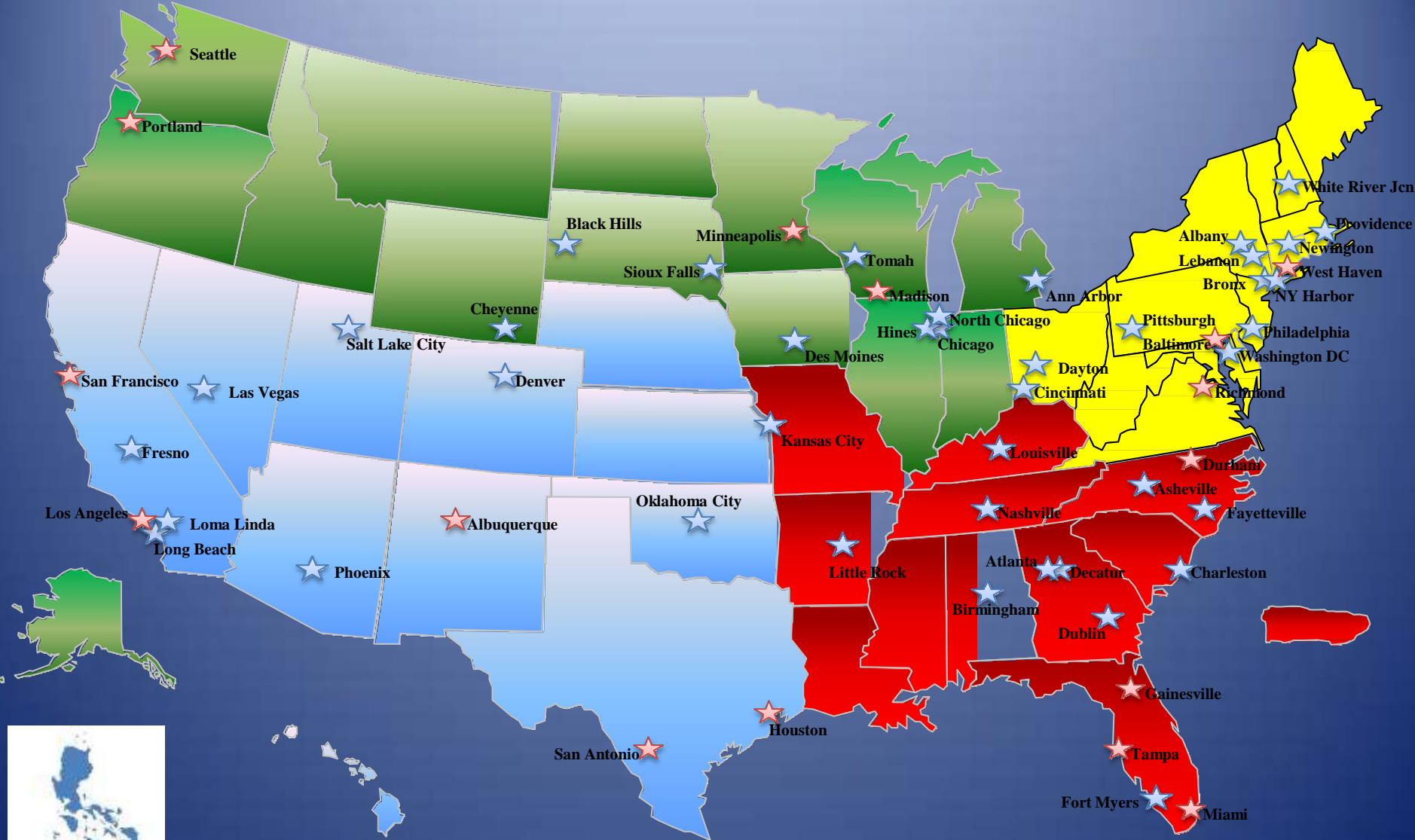
Epilepsy Centers
of Excellence



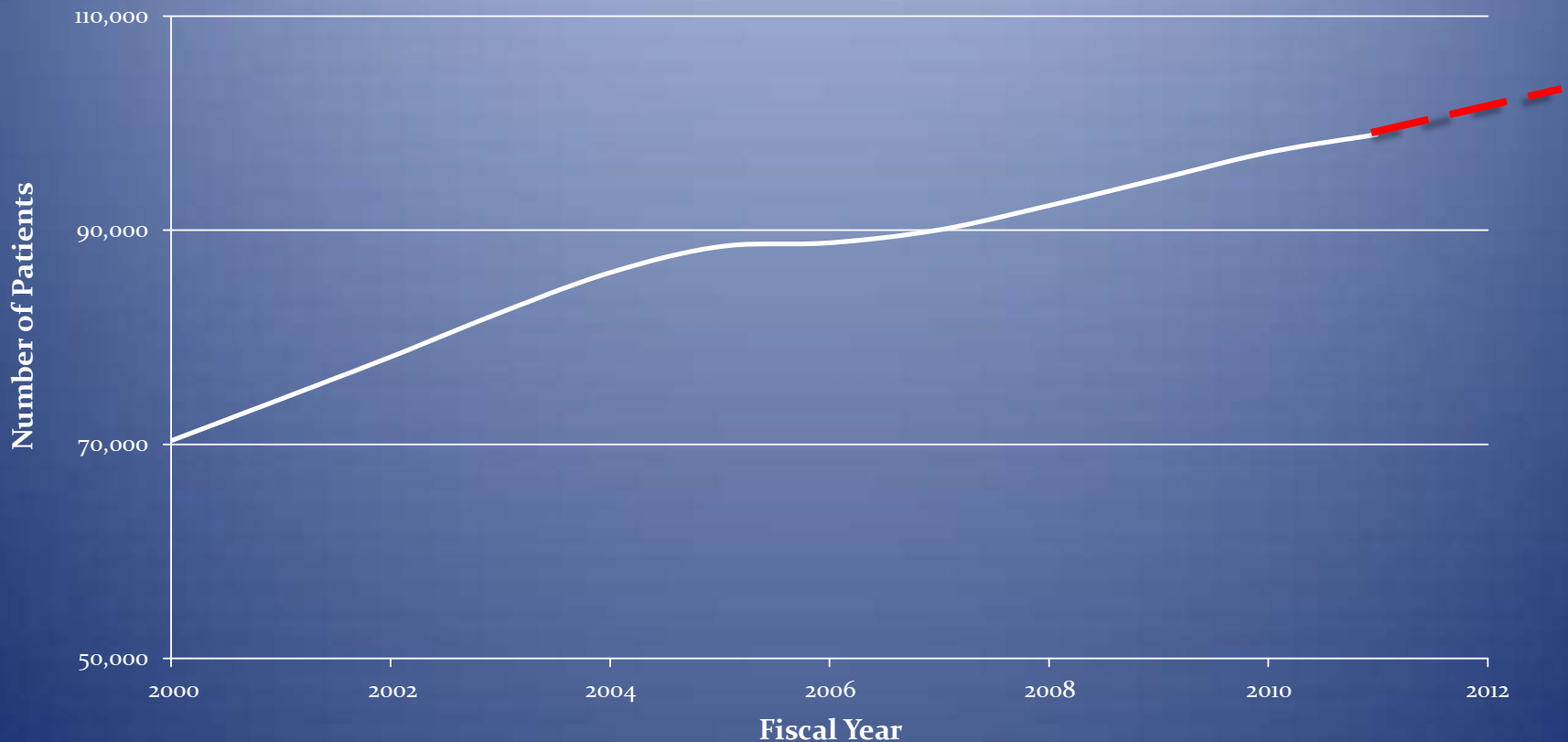
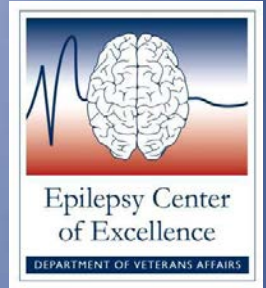
National VA Epilepsy Consortium



VA Epilepsy Center of Excellence



Increasing Number of VA Seizure Patients



Data Source: Office of Specialty Care Transformation

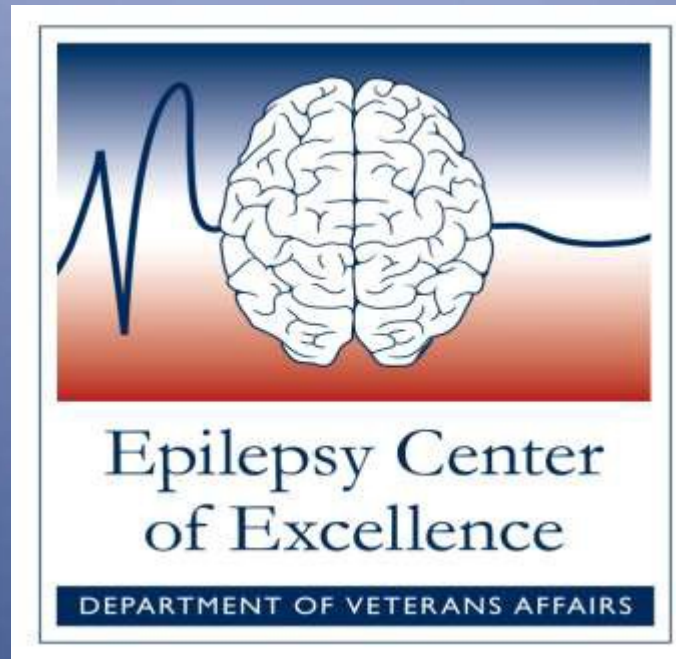
Data collected using ICD-09 codes 345.xx, 780.3, 780.33, 780.39, 780.02, 780.09, 649.40, 649.41, 649.43, 649.44

Post-Traumatic Epilepsy

Veterans Affairs Epilepsy Centers of Excellence

Interagency Collaborative to Advance Research in Epilepsy (ICARE)

June 27, 2012



Karen L. Parko, M.D.

National Director, VA Epilepsy Centers of Excellence

San Francisco VA Medical Center

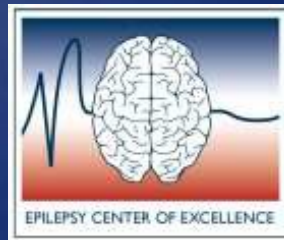
Professor of Neurology, University of California at San Francisco

Post-traumatic Epilepsy (PTE) in the VA

1. Overview of VA PTE Priority Research
2. Ongoing PTE Research
 1. VA
 2. DoD/DARPA
 3. VA Databases
3. Unmet needs in PTE Research
 1. Epidemiological/predictors
 2. Neurosurgical treatments
 3. Psychogenic Non-epileptic seizures
4. Future Collaborative Projects in PTE
 1. PatientsLikeMe
 2. Long-term EEG monitoring in TBI

Major topics of interest in PTE epilepsy research

1. What is the risk of Mild TBI on PTE?
2. Can PTE be prevented after a TBI?
3. Does PTE after Blast injury occur analogously to other forms of PTE after TBI ?
4. How do other TBI factors (cognitive, PTSD, depression) change PTE treatment?
5. What happens with TBI and PTE as the person ages? (Vietnam/Korean War Veterans)
6. What is the relationship of psychogenic non-epileptic seizures (PNES) to TBI and PTSD?
7. What is the relationship of PTE to PTSD?
8. The treatment of PTE is difficult. What can we offer outside AEDs?
9. The VA System of Care for epilepsy is a national system. How do we make it a quality/model system?
10. What are predictors of PTE after TBI outside known risk factors?





Current VA Post-traumatic Epilepsy Research Portfolio

Alan R. Towne, M.D., M.P.H.

Professor of Neurology, Epidemiology and Community
Health, Virginia Commonwealth University Director

ECOE, McGuire VAMC

Colonel, Medical Corps, 29th ID

Post-traumatic seizures

- Traumatic brain injuries are an important cause of epilepsy, accounting for 20% of symptomatic structural epilepsy observed in the general population, and 5% of all epilepsy. TBI is the leading cause of epilepsy in young adults .

Defense and Veterans Brain Injury Center (DVBIC)

TBI Numbers by Severity-All Armed Forces

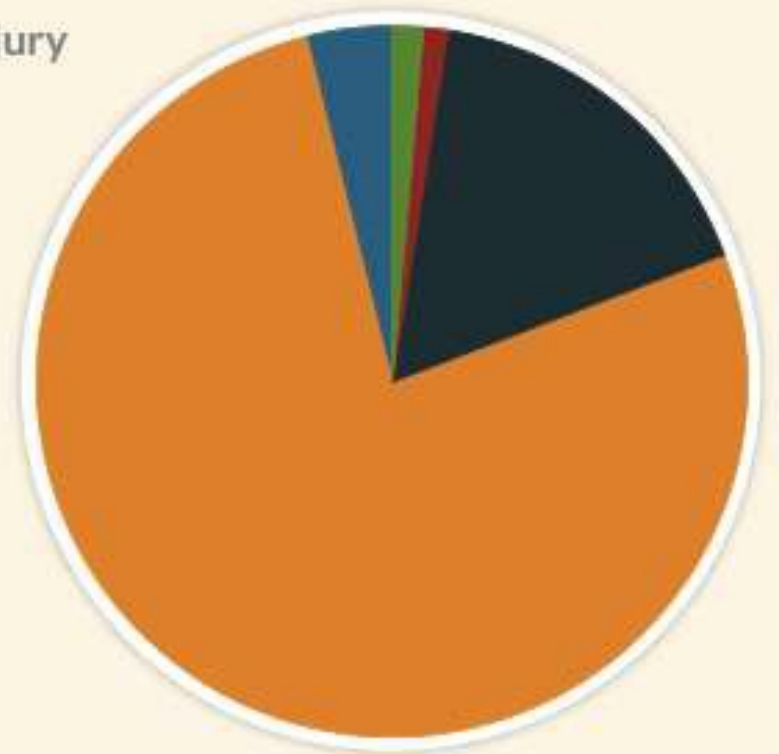


DoD Numbers for Traumatic Brain Injury

'00-'11 Q2 Totals

Penetrating	3,631
Severe	2,288
Moderate	36,752
Mild	169,209
Not Classifiable	8,550

Total - All Severities	220,430
------------------------	---------



Source: Defense Medical Surveillance System (DMSS) and Theater Medical Data Store (TMDS) Prepared by Armed Forces Health Surveillance Center (AFHSC)

DoD Numbers for Traumatic Brain Injury

Incidence by Severity



No. of cases

30,000

25,000

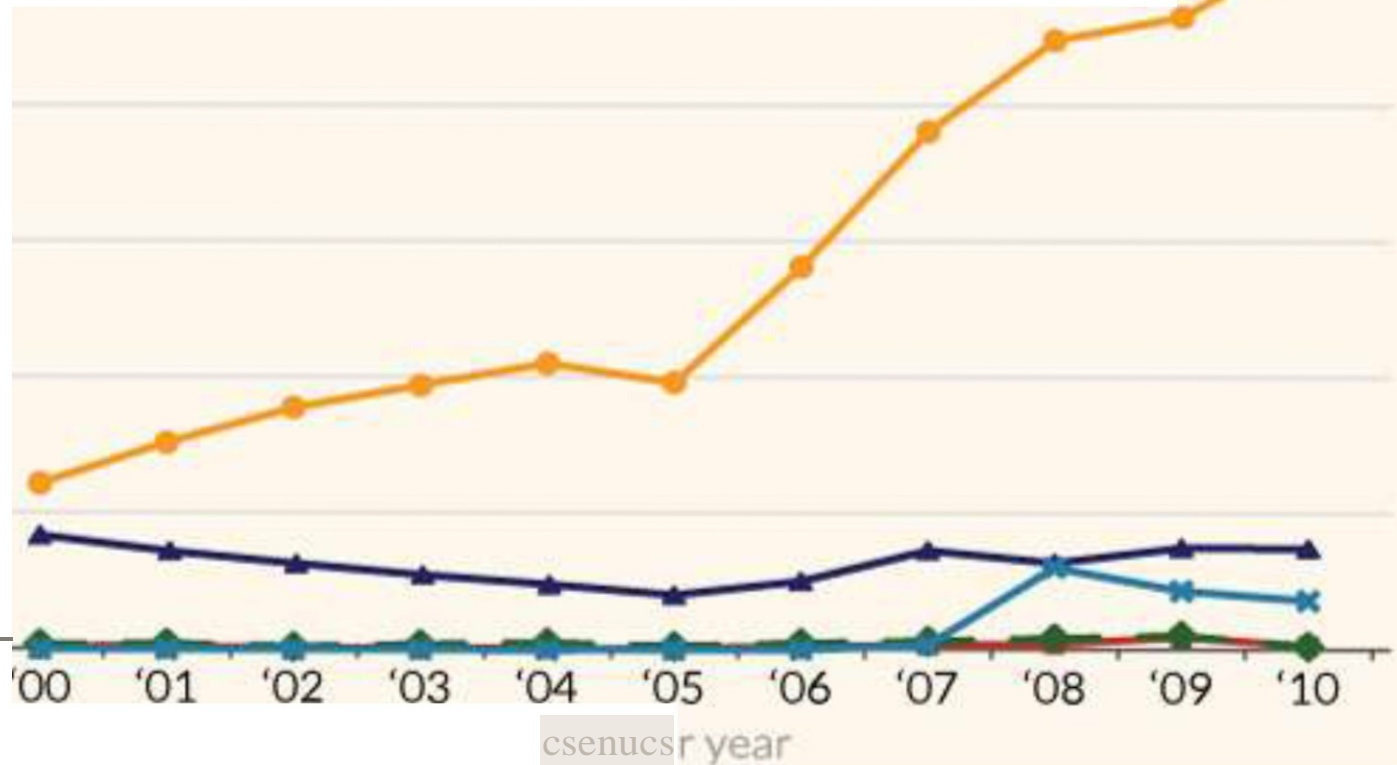
20,000

15,000

10,000

5,000

0



Mild

Moderate

Severe

Penetrating

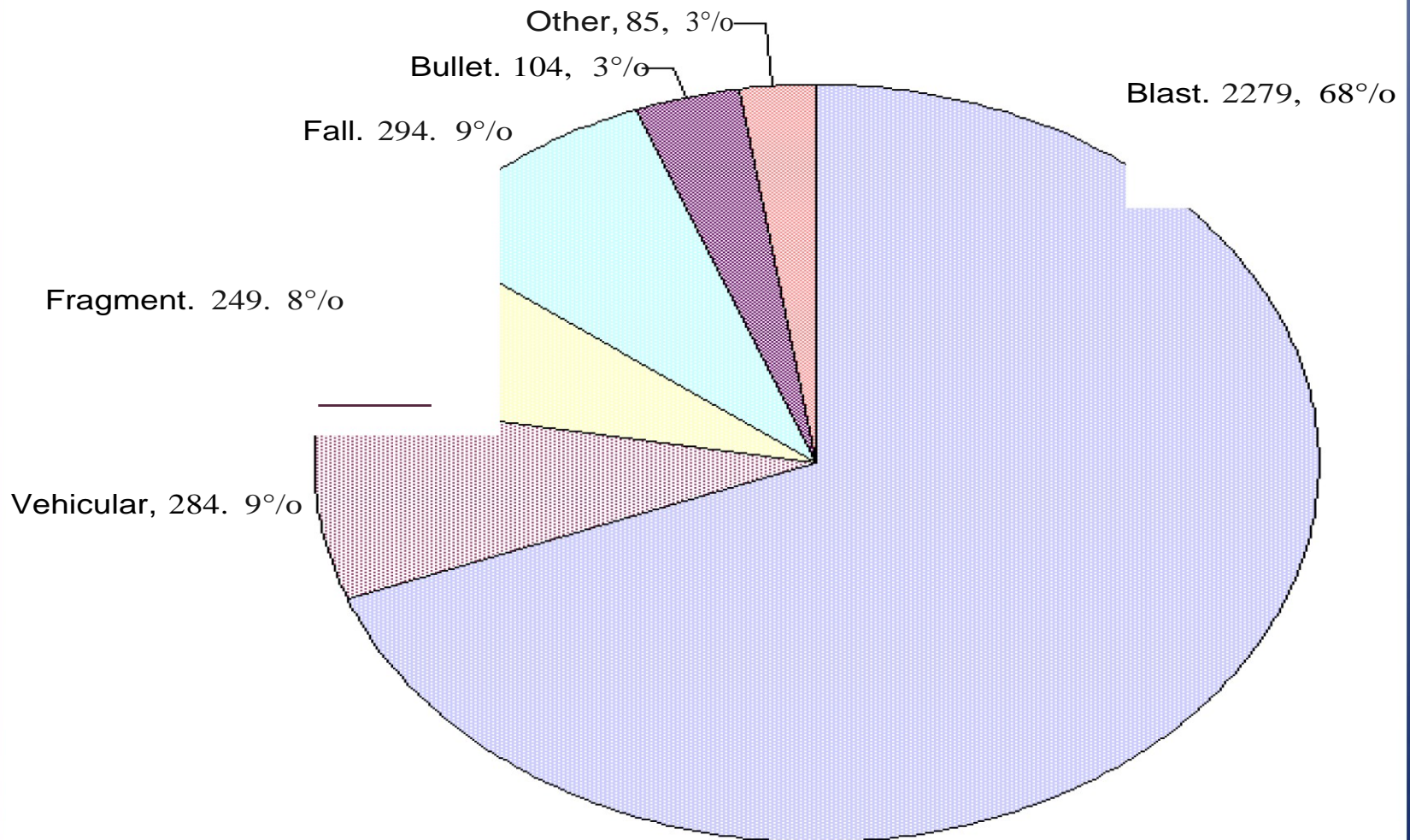
Unclassified

Source: Armed Forces Health Surveillance Center

Updated 16 May 2011

Traumatic Brain Injury

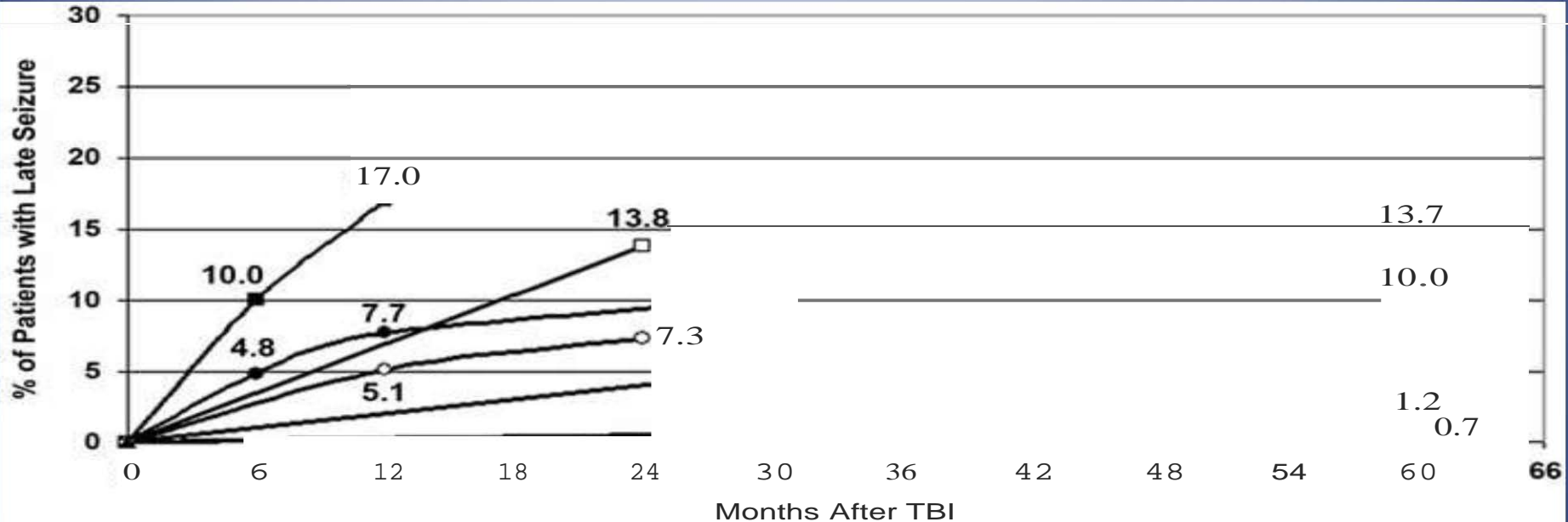
TBI INJURY MECHANISM



Military TBI

- Some experts have estimated the incidence of TBI among wounded service members to be as high as 22.8%. DVBIC lead VA centers (Minneapolis, Palo Alto, Richmond and Tampa) have treated thousands of OIF/OEF patients with TBI.

Cumulative Probability of late unprovoked seizures



...., _	Asikajnen et al (1)		
-O-	Englander et al [2]	---	Ang-eleriet al. [4]
....., _	Annegers et al., mild TBI, peds included [3]		Jennett and Lewin, peds included [5]
-...-	Annegers et al., severe TBI, peds included [3]		Annegers et al., moderate TBI, peds included [3]

Figure.

Cumulative probability of J to $\ln \text{pro}^{\text{J}} \text{Ked sci7ure}$ 1 cr traumatic brain injury (TJ3J) in seven .tudies. Mild to moderate TBI i correlated with lower ri-k of dc \ closing IX..ttroum;ttic epilep.;y (PTI.). Prevalence of Prwa- 10 ,, 17 pc.recent Wllh m* lm* follnw-up peri-od Of 5 y..ar.. p; "(b = ped'turic... 11J ...i..

Blast Injury

- Multifactorial injury mechanism: Primary, secondary, tertiary, quaternary.



Areas for further research in TBI

Seizures and Epilepsy

- Neuroimaging including diffusion tensor imaging
- Genetic factors that may influence PTE (APOE etc.)
- Long-term cognitive outcome and PTE
- Develop modalities to prevent epileptogenesis and prevention of Epilepsy after TBI. Are some interventions better suited?

Areas for further research in TBI Seizures and Epilepsy

- What is the risk of Mild TBI on PTE?
- Does Blast Mechanism differ from other TBI mechanisms?
- How do other TBI factors (cognitive, PTSD, depression) change PTE treatment? Should we have a different approach to treatment?
- What happens with TBI and PTE as the person ages?

Ongoing VA Research Projects

- Genetic factors in TBI and PTE: Partnership with Epilepsy Phenome/Genome Project (EPGP) and Million veterans Program (MVP) genomic program
- Data base for studying TBI and PTE with links to polytrauma centers. Database includes clinic, outpatient and EMU.
- Development of an EMU database involving all centers in the ECOE.
- A pilot and feasibility study: EMU and sleep monitoring for veterans from the OEF/OIF cohort with history of blast-associated mTBI
- Group I Metabotropic Glutamate Receptors and Epileptogenesis
- GABA transporter type 1 (GAT1) function of epilepsy
- Rational polytherapy in the treatment of cholinergic seizures

Ongoing VA Research Projects

- Evaluate the safety and efficacy of a responsive form of neurostimulation to control seizures.
- Prediction, Detection, and Prevention of Posttraumatic Epilepsy and PTSD in Genetically Susceptible Rats
- Traumatic Brain Injury and Posttraumatic Epilepsy: A Prospective Study
- Psychogenic Non-epileptic Seizures in U.S. Veterans
- 2-deoxy-D-glucose Treatment to prevent traumatic brain injury sequelae
- The epidemiology of status epilepticus
- Treatment Of Status Epilepticus: A Translational Proposal

Ongoing VA Research Projects

- The role of dendritic excitability in epilepsy
- Frequency dependence of neocortical excitability and the role of potassium channels

Current DoD Post-traumatic Epilepsy Research

Dr. Ramon Diaz-Arrastia, MD, PhD
Director of Clinical Research, Center for
Neuroscience and Regenerative Medicine
Professor of Neurology
Uniformed Services University of the Health
Sciences

Department of Defense Epilepsy Research Portfolio

- Congressionally Directed Medical Research Programs (CDMRP)
 - 21 Projects since 2001 (15 since 2008)
 - \$15.26 million since 2001 (\$9.73 million since 2008)
- Center for Neuroscience and Regenerative Medicine (CNRM)
 - 2 projects since 2008
 - \$0.8 million committed 2012 - 2014

Proposal Title	Principal Investigator	Institution	Type	FYear Funded	Award Amount
Optogenetic Control of Seizures	CASH, SYDNEY	MASSACHUSETTS GENERAL HOSPITAL	Preclinical	2008	\$725,154.00
Optogenetic Control of Seizures	MAJEWSKA, ANNA	ROCHESTER, UNIVERSITY OF	Preclinical	2008	\$744,015.00
Prediction, Detection, and Prevention of Post-Traumatic Epilepsy and PTSD in Genetically Susceptible Rats	SUTULA, THOMAS P	WISCONSIN, UNIVERSITY OF, MADISON	Preclinical	2008	\$222,750.00
Photoacoustic Imaging of Epilepsy	JIANG, HUABEI	FLORIDA, UNIVERSITY OF	Preclinical	2008	\$2,184,456.00

Proposal Title	Principal Investigator	Institution	Type	FYear Funded	Award Amount
M Current-Based Therapies for Nerve Agent Seizures	KAPUR, JAIDEEP	VIRGINIA, UNIVERSITY OF	Preclinical	2009	\$1,136,247.00
Epilepsy and the Wnt Signaling Pathway	YEE, AUDREY S	COLORADO, UNIVERSITY OF, DENVER, MEDICAL CAMPUS	Preclinical	2009	\$756,982.00
Epilepsy and the Wnt Signaling Pathway	YEE, AMY	TUFTS UNIVERSITY SCHOOL OF MEDICINE	Preclinical	2009	\$421,580.00
JaK/STAT Inhibition to Prevent Post-Traumatic Epileptogenesis	BROOKS-KAYAL, AMY R	COLORADO, UNIVERSITY OF, DENVER, MEDICAL CAMPUS	Preclinical	2010	\$705,887.00

Proposal Title	Principal Investigator	Institution	Type	FYear Funded	Award Amount
New Treatments for Drug-Resistant Epilepsy that Target Presynaptic Transmitter Release	STANTON, PATRIC K	NEW YORK MEDICAL COLLEGE	Preclinical	2010	\$399,940.00
New Treatments for Drug-Resistant Epilepsy that Target Presynaptic Transmitter Release	GARRIDO-SANABRIA, EMILIO	TEXAS, UNIVERSITY OF, AT BROWNSVILLE	Preclinical	2010	\$443,219.00
Whole Brain Networks for Treatment of Epilepsy	SAKAIE, KEN	CLEVELAND CLINIC FOUNDATION	Clinical	2010	\$99,016.00
JaK/STAT Inhibition to Prevent Post-Traumatic Epileptogenesis	SMITH, BRET N	KENTUCKY, UNIVERSITY OF	Preclinical	2010	\$354,432.00

Proposal Title	Principal Investigator	Institution	Type	FYear Funded	Award Amount
Mechanism and Therapy for the Shared Susceptibility to Migraine and Epilepsy after Traumatic Brain Injury	BRENNAN, KEVIN C	UTAH, UNIVERSITY OF	Preclinical	2010	\$1,036,848.00
A New, Quantitative EEG Technique for Prediction of Post-Traumatic Epilepsy in Individual Subjects after Traumatic Brain Injury	TREIMAN, DAVID M	ST. JOSEPH'S HOSPITAL AND MEDICAL CENTER	Preclinical and Clinical	2010	\$300,000.00
Targeting Microglia to Prevent Post-Traumatic Epilepsy	BARTH, DANIEL S	COLORADO, UNIVERSITY OF, BOULDER	Preclinical	2010	\$920,447.00

Proposal Title	Principal Investigator	Institution	Type	FYear Funded	Award Amount
New Treatments for Drug-Resistant Epilepsy that Target Presynaptic Transmitter Release	Garrido-Sanabira, Emilio and Stanton, Patrick	University of Texas, Brownsville and New York Medical College	Preclinical	2010	\$843,159
Quantitative EEG for Prediction of Post-traumatic Epilepsy after TBI	Treiman, David M.	St. Joseph's Hospital and Medical Center	Preclinical and Clinical	2010	\$300,000

Proposal Title	Principal Investigator	Institution	Type	FYear Funded	Award Amount
JaK/STAT Inhibition to Prevent Post-Traumatic Epileptogenesis	SMITH, BRET N	KENTUCKY, UNIVERSITY OF		2010	\$354,432.00
Mechanism and Therapy for the Shared Susceptibility to Migraine and Epilepsy after Traumatic Brain Injury	BRENNAN, KEVIN C	UTAH, UNIVERSITY OF		2010	\$1,036,848.00
A New, Quantitative EEG Technique for Prediction of Post-Traumatic Epilepsy in Individual Subjects after Traumatic Brain Injury	TREIMAN, DAVID M	ST. JOSEPH'S HOSPITAL AND MEDICAL CENTER		2010	\$300,000.00
Targeting Microglia to Prevent Post-Traumatic Epilepsy	BARTH, DANIEL S	COLORADO, UNIVERSITY OF, BOULDER		2010	\$920,447.00

CNRM Projects

Proposal Title	Principal Investigator	Institution	Type	FYear Funded	Award Amount
One Carbon Metabolism Markers in Post-Traumatic Epilepsy	Sher, Ann	USUHS	Clinical	2012	\$400,000
NR2B-selective antagonist to ameliorate posttraumatic epileptogenesis and its associated comorbidities	Bausch, Suzanne	USUHS	Preclinical	2012	\$400,000

CNRM Project: One-Carbon Metabolism Markers in Post-Traumatic Epilepsy

- Common and well-studied MTHFR C677T variant is a biologically plausible genetic risk factor for seizures or epilepsy
 - TT carriers have elevated homocysteine, a pro-convulsant
 - TT genotype linked with migraine with aura, a comorbid condition for epilepsy
 - TT genotype / homocysteine linked with risk of alcohol withdrawal seizures
- Gene-association study based on 1600 subjects identified through DoD Serum Repository*

*Funded by Comprehensive Neuroscience Program

Results from First Study

- Able to genotype ~85% of subjects using archived serum
- Odds of epilepsy increased in TT vs CC carriers:
 - Overall (all epilepsy): OR=1.52 [1.04-2.22], p=0.031
 - Post-traumatic epilepsy: OR=1.92 [1.01-3.64], p=0.046
- Follow-on study planned (CNRM):
 - Replicate findings in new cohort of PTE cases / controls
 - Measure pre-diagnosis serum markers of impaired folate metabolism for mechanistic data
- Possible implications:
 - Will allow us to identify subjects at increased risk of neurological injury following head trauma
 - Clinical trial of pre-injury folic acid supplementation as neuroprotective agent in those at high risk of head trauma

NR2B-selective antagonist to ameliorate posttraumatic epileptogenesis and its associated comorbidities

Suzanne B. Bausch, Ph.D.

Previous work:

NR2B-selective antagonist chosen from screen of various NMDAR antagonist classes in in vitro posttraumatic epileptogenesis model

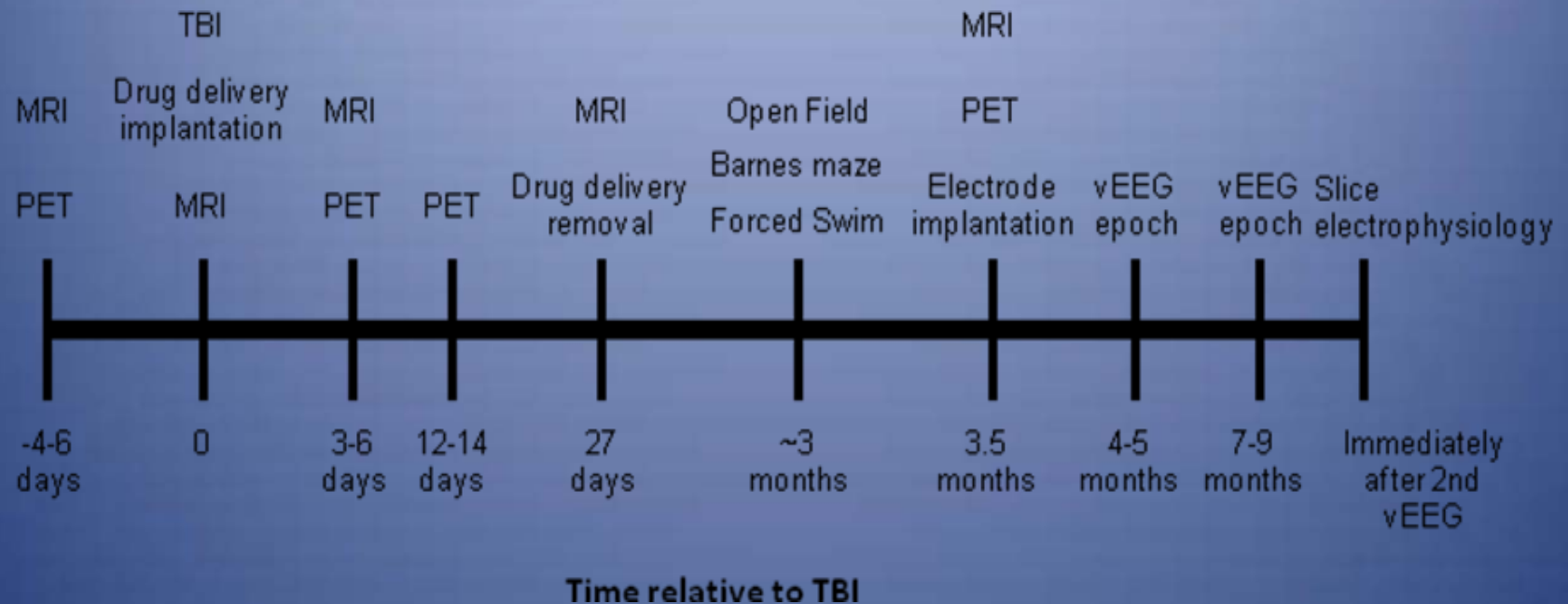
Chronic treatment with NR2B-selective antagonist after TBI shown to reduce susceptibility to chemoconvulsant-induced seizures

CNRM funded project:

Our *hypothesis* is that NR2B-selective antagonist will retard posttraumatic epileptogenesis, hippocampal atrophy, metabolic changes, memory dysfunction, depression, and cortico-hippocampal hyperexcitability.

Proof of principle -

Severe lateral fluid percussion injury in male SD rats
Drug delivery (single dose, icv) for 21 d beginning 1 hr after TBI



Time relative to TBI

Document effects of NR2B antagonist on TBI-induced:

1. hippocampal atrophy & metabolic changes (MRI and [^{18}F] FDG PET)
2. motor function, memory dysfunction, & depression (behavioral tests)
3. spontaneous recurrent seizures (video EEG monitoring)
4. functional changes in cortico-hippocampal hyperexcitability (60 MEA recordings)

Research using existing VA and other available data

Past, Present, Future

Mary Jo Pugh, PhD

Research Health Scientist

South Texas Veterans Health Care System

Associate Professor

Department of Epidemiology and Biostatistics

Department of Medicine, Geriatrics and Gerontology

University of Texas Health Science Center at San Antonio

Existing VA Data: What is Available?

- Administrative Data
 - National SAS Medical Data Sets
 - Inpatient Data
 - Outpatient Data
 - National VA Pharmacy Data
- Clinical Data
 - TBI Screening Data
- Electronic Medical Record
- National Surveys of Veterans

Past Work

- Administrative Data and National Veteran Surveys
 - Impact of Epilepsy on Veterans' Quality of Life
- Administrative Data: Epilepsy Epidemiology
 - Prevalence of Epilepsy in Older Veterans
 - Risk Factors for New-onset Epilepsy in Older Veterans

Past Work cont.

- Pharmacoepidemiology and Outcomes
 - Seizure Medication Treatment Patterns for Older Veterans
 - Changes in Choice of Seizure Medications Over Time
 - Potential Drug-Interactions in Older Veterans
 - Outcomes Associated with Potential Drug Interactions in Older Veterans

Past Work cont.

- Quality Measures
 - Quality in Epilepsy Treatment (QUIET) VA
 - Adapted QUIET measure to the VA integrated medical system
 - Most important additions:
 - Specific recommendations for referral to epilepsy specialty care:
 - IF a patient with epilepsy continues to have seizures after three months of care by a primary care provider, further assessment by a neurologist should be conducted.
 - IF a patient continues to have seizures after 12 months of appropriate care by a general neurologist, THEN the patient should receive a referral to an epilepsy specialist.

Current Research

- **Restructuring Epilepsy Care: Organizational Dynamics and Quality**
 - Benchmark Quality of Care using QUIET-VA measure
 - 2008 (prior to ECOE)
 - 2011 (mid ECOE implementation)
 - 2014 (After ECOE implementation)
 - Catalog changes in structures and processes of care and the relationship with quality.
 - Identify Barriers and Facilitators to Providing High Quality Epilepsy Care
 - Goal: Identify Targets for Intervention to Improve Care

Current Research cont.

- *Trajectories of Resilience and Comorbidity Clusters in OEF-OIF Veterans (TRACC OEF-OIF)*
 - Identify Comorbidities and Trajectories of Comorbidity Over Time
 - Identify TBI diagnoses
 - Incorporate TBI Screening Database
 - Identify Epilepsy using Validated Algorithms
 - Predictive Models of Post-traumatic Epilepsy
 - Identify Treatment Patterns and Changes Over Time

Current Predictive Model: Prevalent Epilepsy

Predictors of Prevalent Epilepsy in FY10	OR	95% CI
Penetrating TBI	20.2	13.0-31.4
Severe TBI	6.7	4.7-9.5
Moderate TBI	2.6	2.4-2.9
Mild TBI	1.8	1.6-2.0
Less specific history of TBI or unclassified	2.4	2.0-2.8
PTSD	1.190	1.1-1.3

Controlling for age, sex, race, stroke, cardiac disease, psychiatric diagnoses, cognitive impairment/ dementia diagnoses, and diagnoses indicative or more severe head injury (e.g., amputation, spinal cord injury, burn)

Future Projects

- Collaborative VA-DoD Study linking data from the TRACC Study to the Joint Theatre Trauma Registry and other DoD data (EMR and Chart Abstraction) to study the natural history of epidemiology of mild, moderate and severe TBI with regard to epilepsy.

Preventing Epilepsy after TBI: the need for clinical trials

Marc Dichter, MD, PhD

Chair, National Professional Advisory Board ECoE

Professor of Neurology and Pharmacology

Director of the Mahoney Institute of Neuroscience

University of Pennsylvania

TBI and Post-traumatic Epilepsy Statistics and Risks

- ~400,000 returning veterans from gulf wars with TBI
 - ~10,000 – 20,000 new cases of PTE
- Civilians get TBI and PTE also
 - ~1.5 million civilian cases of TBI /yr in US
 - 80% mild
 - 10% moderate = ~15,000 new cases of PTE/yr
 - 10% severe = 37,500 – 75,000 new cases PTE/yr

Current clinical protocol for preventing epilepsy after TBI



Current status of antiepileptogenesis

- Off the radar screen for a long time
- Phenytoin doesn't work *
- VPA doesn't work *
- MgSO_4 doesn't work *
- No evidence that CBZ or phenobarbital are effective, but data are not as strong
- Research in this area has been slow

(* based on one randomized controlled double blind study each)

Antiepileptogenesis vs Recovery of Function

- Data from both TBI and ischemia models
 - Some AEDs may retard recovery (e.g. benzodiazepines and barbiturates)
- “Soft” human studies suggest treatment with benzodiazepines or barbiturates after stroke is associated with less recovery
- Role of seizures during recovery is complex
 - May be harmful or may promote recovery depending on model and timing

Limitations with current technology

- We cannot detect small, highly localized seizures with surface EEGs
- We cannot monitor electrophysiological activity in deep structures
- We cannot continuously monitor EEG over prolonged periods



Surface EEG

Depth EEG

Focus on post-TBI epileptogenesis

- Very little experimental data to support major clinical investment but the field is beginning to move
- Some proof of principle data now available
 - Local cooling
 - mTOR inhibitors
- However, magnitude of the problem, with both civilian and military TBI is very large
- Need to start developing prototype clinical paradigms to allow clinical investigation to proceed in parallel with enhanced experimental approaches

Issues for a clinical trial protocol for preventing epilepsy after TBI – It's not easy

- Which patients
 - Moderate to severe TBI (e.g. GCS ≤ 12)
 - Blood in the brain or SDH
 - Depressed skull fracture
- How large a sample
- What agent to use
- How quickly to treat
 - Hyperacute (hours)
 - Acute (1-3 days)
 - Subacute (>3 days) – during “latent period”
- What kind of EEG monitoring
- Which endpoints
- How much follow up
- How much functional assessment during recovery

A proposal for a clinical trial protocol for preventing epilepsy after TBI

- Create ongoing consortium of groups in trauma centers
- Develop funding source for long term studies with new protocols ready to roll out when old ones fail
 - No latency
 - No downtime
 - No dispersal of personnel and expertise
- Try to make study as cost-effective as possible
- Continuous data mining
 - Outcomes
 - Surrogate markers
- Ongoing interaction with basic neuroscientists to seek new treatment options

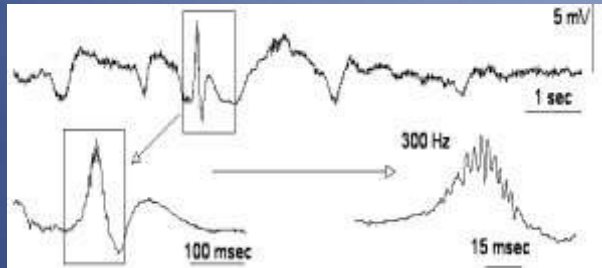
Advantages of early clinical trials

- Experience with infrastructure
- Develop optimum protocols
- Better epidemiology of risk
- Collection of biomarkers
- Development of new tools
- ➔ • Availability of experienced investigator teams as new developments emerge from the laboratory
- ➔ • Establishment of network of experienced investigators
 - Influence the directions of laboratory studies
 - Development of alternative funding sources
- ➔ • Stimulation of anti-epileptogenesis trials in other areas of risk

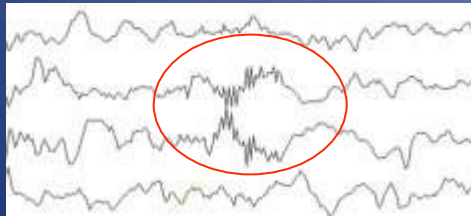
A modest proposal for future antiepileptogenic studies

Implantable electrodes
with Intelligent device

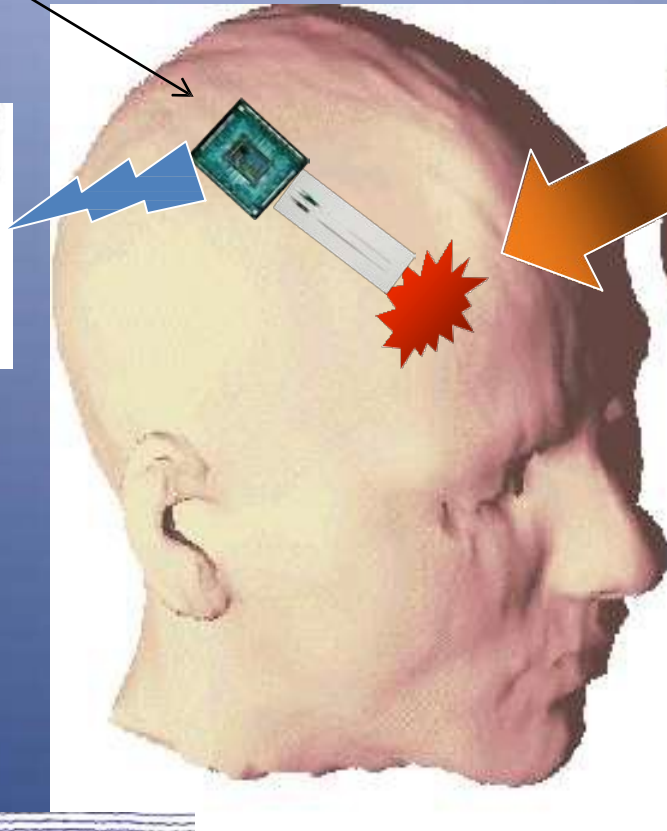
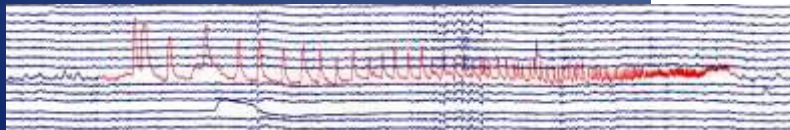
Spikes



HFOs

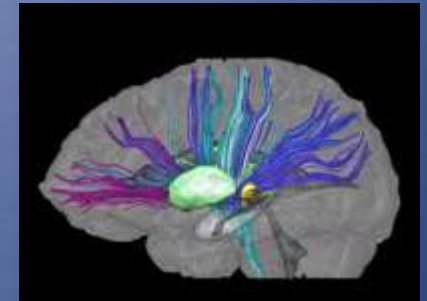


Subclinical seizures



Trauma

Imaging



Proteomics



VA usage patterns of neurosurgical treatment modalities for PTE

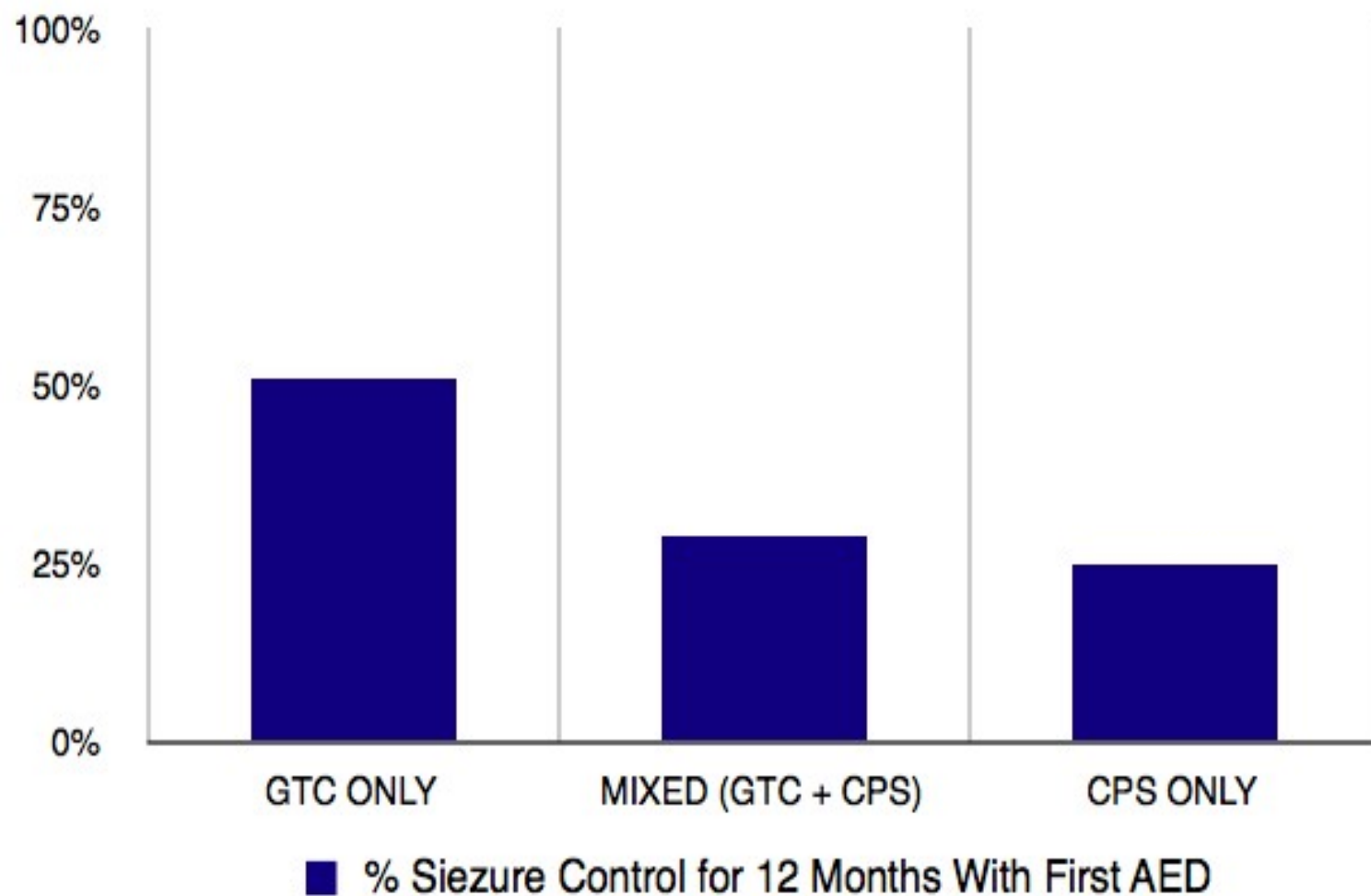
Karen L. Parko, M.D.

National Director, VA Epilepsy Centers of Excellence

San Francisco VA Medical Center

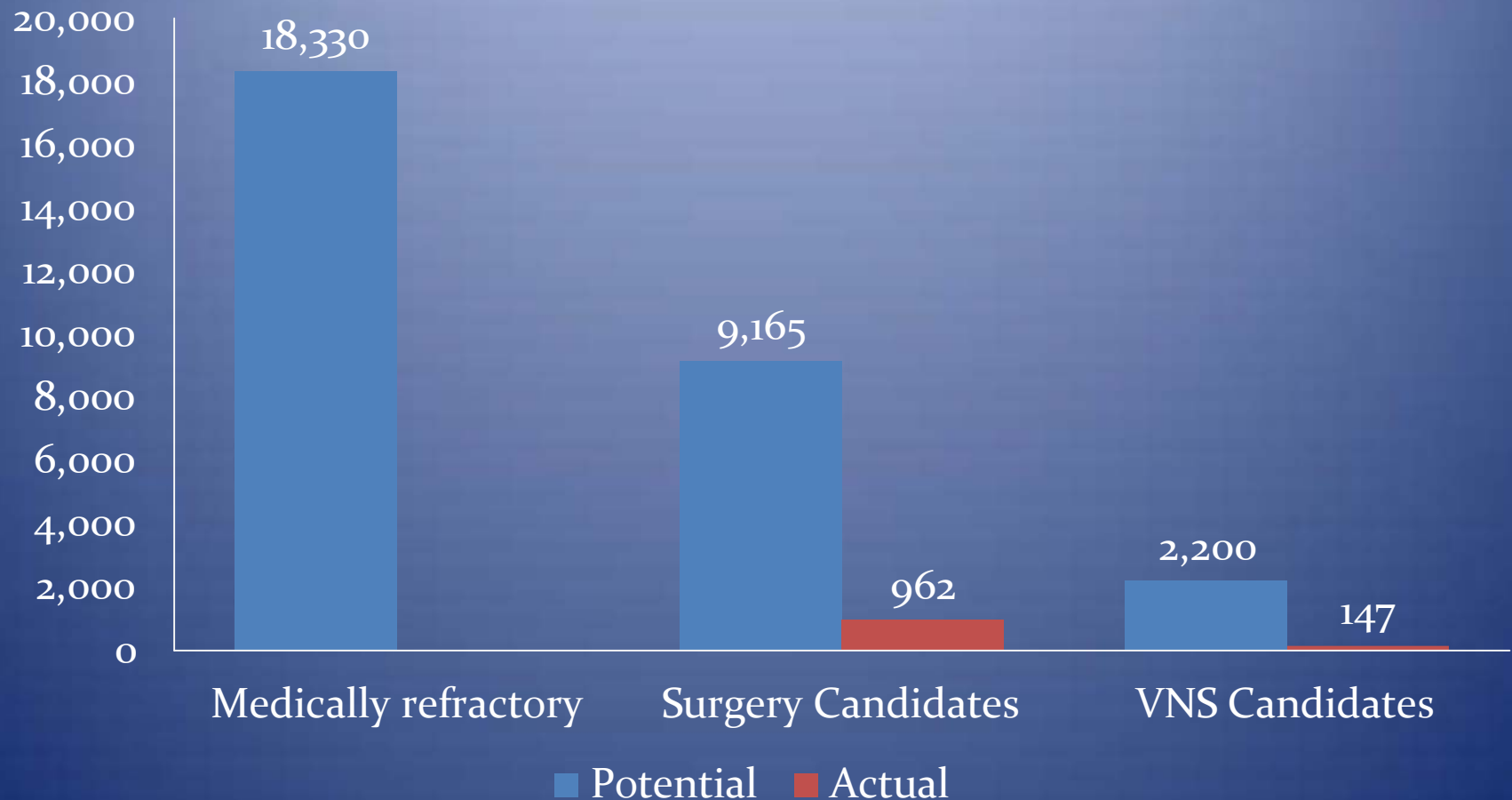
Professor of Neurology, University of California at San
Francisco

Prognosis for Control of Symptomatic Focal Epliepsy in two VA Mulitcenter Studies



Surgical Care of VA Patients

(Less than 10% of Veterans receive available surgical therapies)



PNES in Veterans and its relationship to TBI and PTSD

Hamada Hamid, DO, MPH

Co-Director

VA Epilepsy Center of Excellence in West Haven, CT

Instructor in Neurology and in Psychiatry

Yale School of Medicine

Psychogenic Non-Epileptic Seizures (PNES)

- Somatization disorders constitute a large burden of disease in US Health System
- PNES provides a model to study a bio-psycho-social approach to somatization
- The VA provides an opportunity to explore integrative health care models of service:
 - neurology/mental health/primary care partnerships
 - tele-health consultation and service

PNES

- >70% of people with PNES receive anti-epileptic Rx
- Misdiagnosis costs of Epilepsy costs >\$10,000 per patient per year. Costs reduce by 84% after diagnosis of PNES is made
- QOL in PNES is poor even after diagnosis is provided

PNES

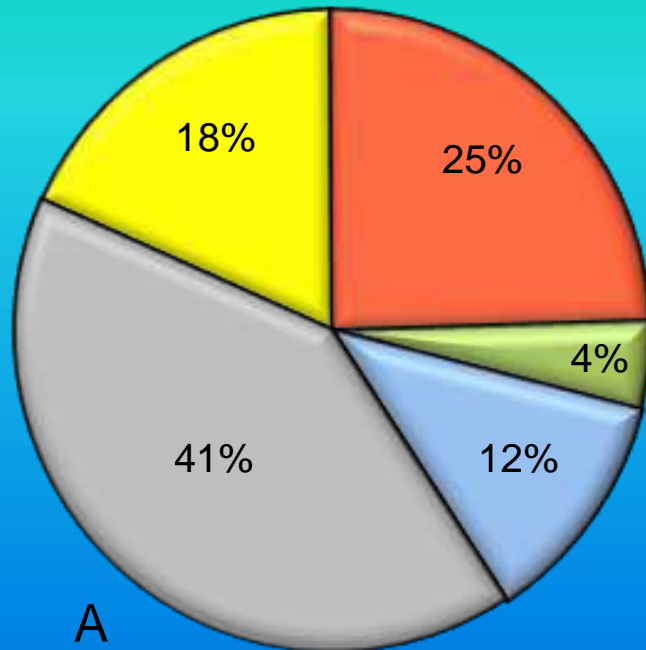
- After VEEG diagnosis:
 - 40% will go into seizure remission for a few months
 - 20% will increase seizure frequency
 - Long term (1-10 years) 70% will relapse
 - Kids have better outcomes
- Predictors of poor outcome
 - Depression, anxiety, personality disorder

PNES: U.S. Veterans

- What is unique about U.S. Veterans?
 - Predominantly younger, male
 - Have good access to primary care and mental health
 - Larger prevalence of PTSD, TBI
- What is unique about the VA?
 - National database
 - Advanced Clinical Bioinformatics Program
 - Integrated models of care (across state lines)
 - VA ECoE Collaborative Research Network

Veterans

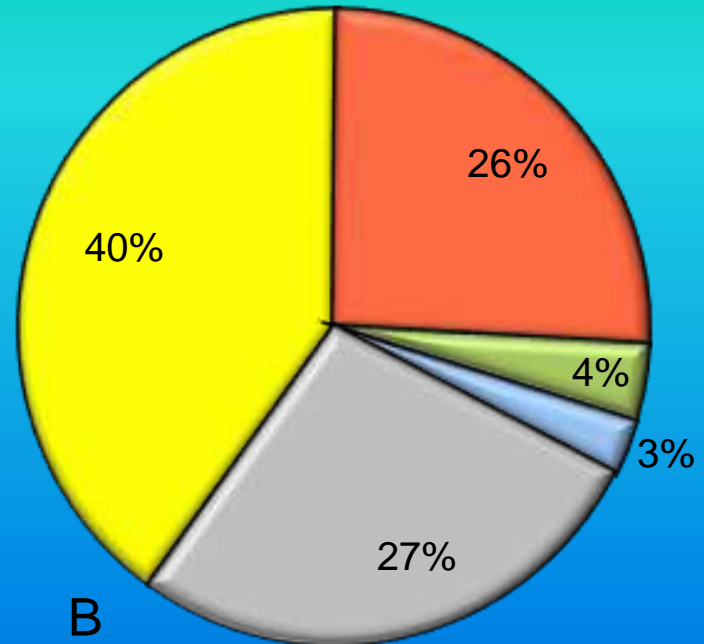
(N=203)



A

Civilians

(N=726)



B

■ Epilepsy ■ PNES ■ Mixed ■ NES Other ■ Nondiagnostic

PNES – Psychogenic non-epileptic seizures

ES – Epileptic seizures

NES other – Syncope, parasomnia, other

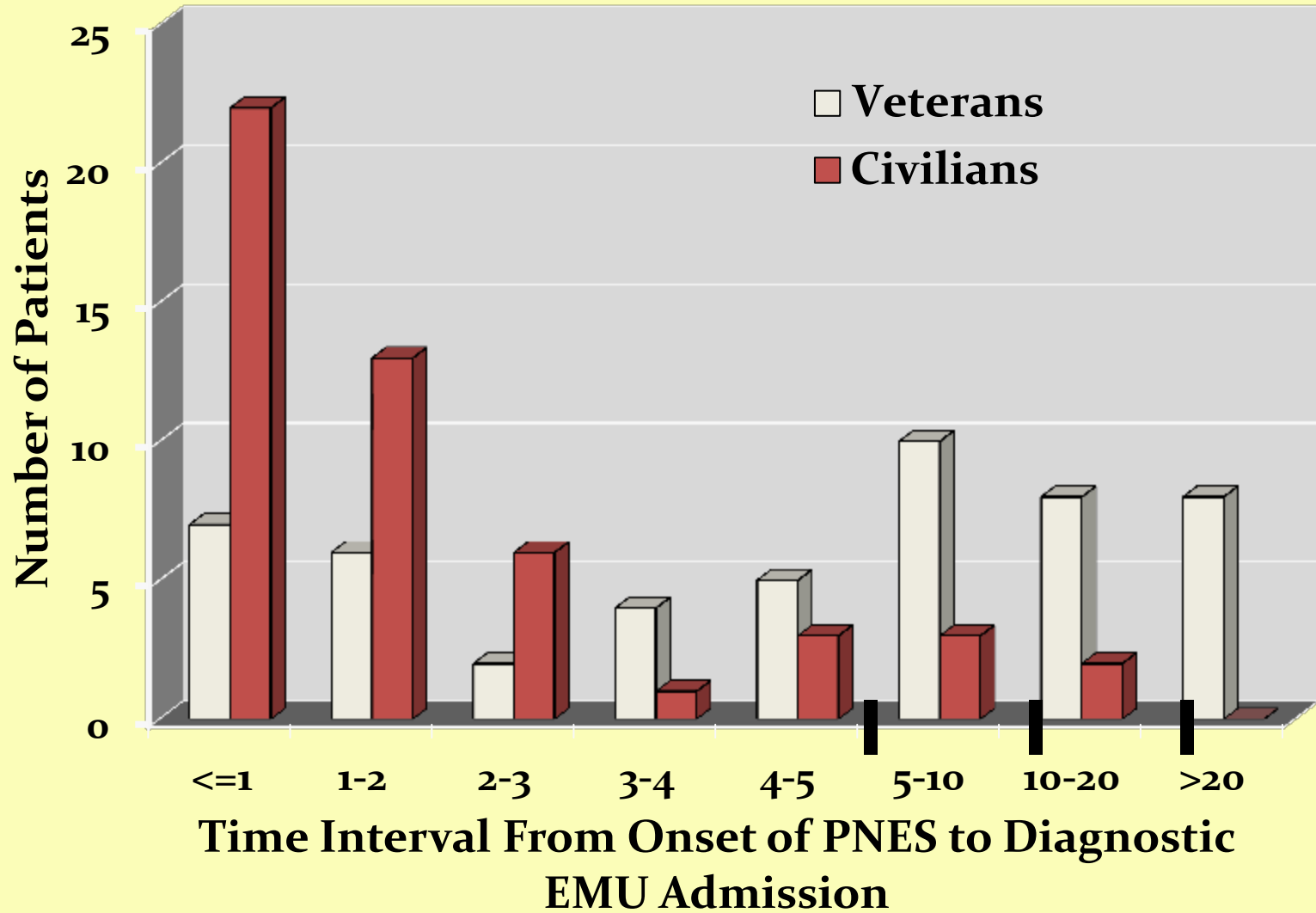
Mixed – PNES + ES

Salinsky et al

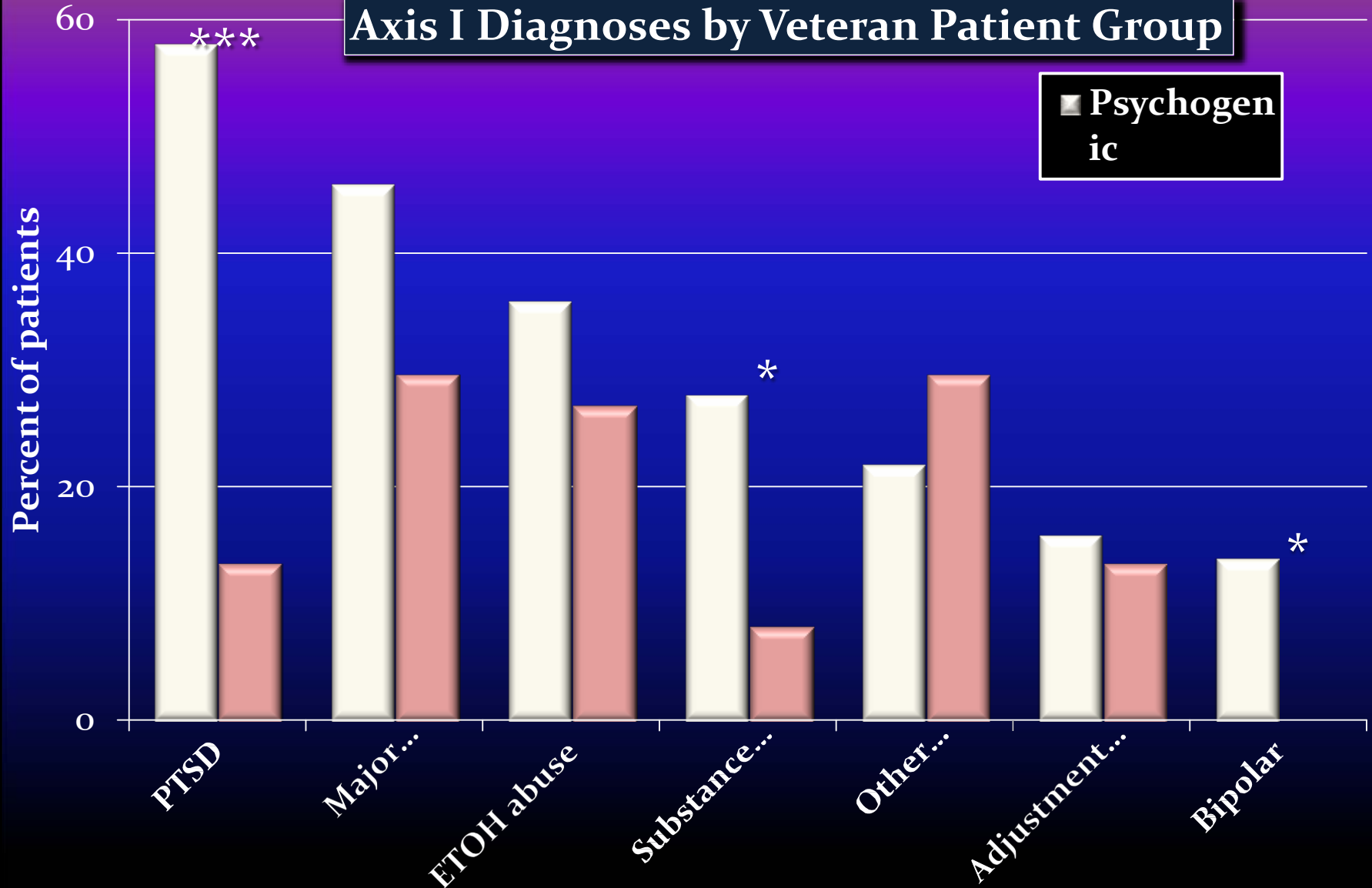
Psychogenic seizures

Veterans Compared to Civilians

	Veterans	Civilians	P value
Cumulative AED-Years	4.0 (0-50)	1.0 (0-30)	<0.01
Onset of Spells to Diagnosis (median months)	60.5 (3-408)	12.5 (2-144)	<0.001
Attributed to TBI	58%	26%	<0.01



Axis I Diagnoses by Veteran Patient Group



*** $p < 0.001$ * $p < 0.05$

Includes all diagnoses found in >10% of patients with PNES or ES

Future Research in PNES

- Neurobiology of PNES
 - Sensory Uncoupling?
 - Dysfunctional Neural Networks?
- What is the relationship between TBI, PTSD and Dissociation?
- What are the psychiatric etiologies associated with PNES in veterans?
- How can we identify PNES earlier in Veterans?
- How should we treat PNES?

Current Clinical Trials

- LaFrance (2009)
 - CBT pre and post: 11/17 (64%) Seizure free
 - Improvement in:
BDI, QoL Epilepsy Scale, Clinical Global Impressions, Dissociative Experience Scale, Barrett Impulsivity Scale, Family Assessment Device, Coping method most used
- Goldstein (2010)
 - 66 PNES randomized to CBT vs SMC
 - Primary outcome: Seizure frequency at 3 and 6 month follow up after completion
 - No Improvement: Depression, Anxiety, ED visits, Medications

Ongoing VA Projects

- Develop Natural Language Processing tool to Identify PNES in Electronic Medical Record
- National VA Database QOL and Utilization of Services Study
- Developing Tele-Video CBT Program for Veterans with PNES
- PNES and Psychiatric Morbidity Study



VA Partnership Research Updates for ICARE 2012

Arianne Graham, MBA
Business Development
PatientsLikeMe

What is PatientsLikeMe?

An online network of 150,000+ patients seeking to connect with others like them for personalized learning and support

You have questions about your disease — but you also have answers for others. Change your life while helping others change theirs.



By learning from **other patients like you...**

- In **Forum Discussions**
- Through **Private Messages**
- From **Profile Comments**

and seeing the **community experience...**

- Browse **Symptom Reports**
- Explore **Treatment Reports**
- Check out **Treatment Evaluations**

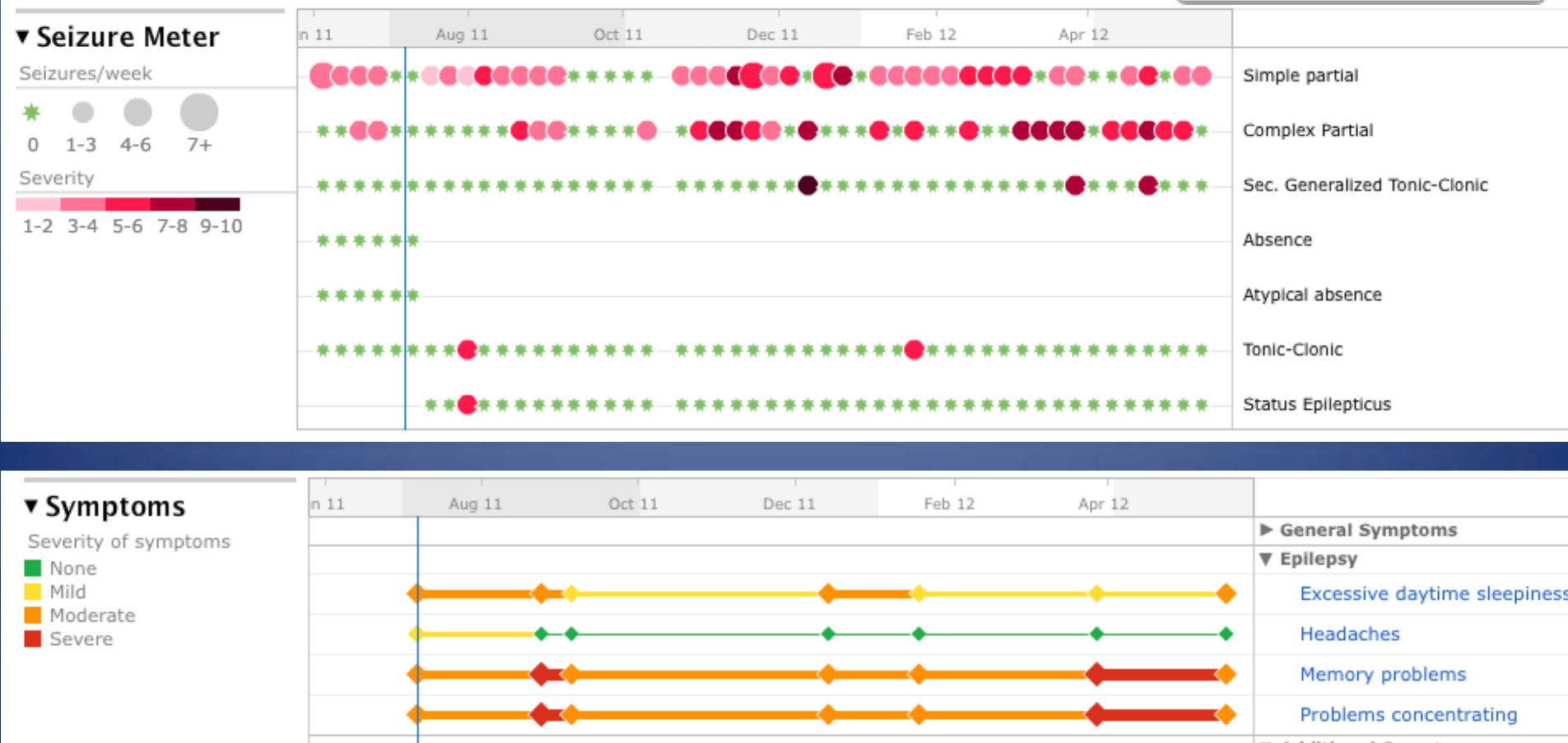
YOU can take control of your disease.

- **Profile charts** let you see how your treatments affect your health over time
- **Doctor Visit Sheets** help you improve your discussions with your doctors

How do patients use PatientsLikeMe?

Patients create online health profiles using validated scales and innovative instruments that longitudinally capture their experiences with their disease

Example: An epilepsy patient's profile on PatientsLikeMe



Why do patients use PatientsLikeMe?

PatientsLikeMe helps its members find others like them and aggregates the data they share into population statistics that contextualize their experience

Is my epilepsy experience normal for someone like me? What does *normal* mean?

How do other patients like me treat their epilepsy? What are their results?



What is it like to have Epilepsy?

Common Symptoms

Patients' Latest Severity

Excessive daytime sleepiness (somnolence)



Headaches



Memory problems



Problems concentrating



What do patients take to treat Epilepsy and its symptoms?

Commonly prescribed and frequently used treatments

Treatment name	Efficacy	Overall rating of side effects	# of Evaluations
Levetiracetam			319
Lamotrigine			221
Carbamazepine			161
Topiramate			153
Phenytoin			127
Divalproex sodium			120
Zonisamide			67
Lacosamide			64
Oxcarbazepine			61

What does PatientsLikeMe produce?

The longitudinal data shared by thousands of patients is then de-identified and used with industry partners to generate new real-world evidence

Original Paper

Sharing Health Data for Better Outcomes on PatientsLikeMe

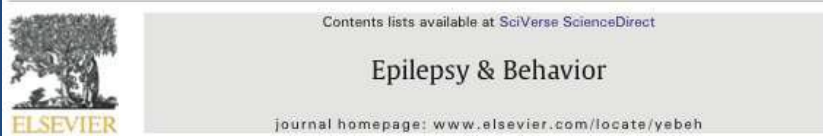
Paul Wicks, PhD; Michael Massagli, PhD; Jeana Frost, PhD; Catherine Brownstein, PhD; Sally Okun, RN; Timothy Vaughan, PhD; Richard

PatientsLikeMe Inc., Research

Abstract

Background: Patients share their experience characteristics, and learn from other patients answer the question

Objective: Using a computational



Perceived benefits of sharing health data between people with epilepsy on an online platform

log^b, Catherine Brownstein^a,

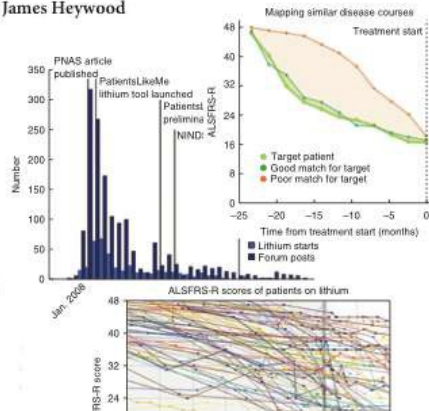
computational BIOLOGY

ANALYSIS

Accelerated clinical discovery using self-reported patient data collected online and a patient-matching algorithm

Paul Wicks, Timothy E Vaughan, Michael P Massagli & James Heywood

Patients with serious diseases may experiment with drugs that have not received regulatory approval. Online patient communities structured around quantitative outcome data have the potential to provide an observational environment to monitor such drug usage and its consequences. Here we describe an analysis of data reported on the website PatientsLikeMe by patients with amyotrophic lateral sclerosis (ALS) who experimented with lithium carbonate treatment. To reduce potential bias owing to lack of randomization, we developed an algorithm to match 149 treated patients to multiple controls (447 total) based on the progression of their disease course. At 12 months after treatment, we found no effect of lithium on disease progression. Although observational studies using unblinded data are not a substitute for double-blind randomized control trials, this study reached the same conclusion as subsequent randomized trials, suggesting that data reported by patients over the internet may be useful for accelerating clinical discovery and evaluating the effectiveness of drugs already in use.



to share data between patients to improve response period, 221 patients with epilepsy completed a survey about benefits they perceived. know anyone else with epilepsy with whom they could connect. Perceived benefits included: better understanding of symptoms (59%), gaining a better understanding of treatments (55%). Number of benefits perceived, $F(4,216) = 8.173, P < 0.001$. Patients with epilepsy reported by populations with other diseases. Perceived benefits of sharing health data between people with epilepsy on an online platform

© 2011 Elsevier Inc. All rights reserved.

these may be related to using to evaluate the

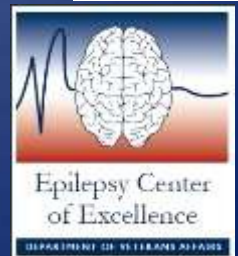
using to evaluate the



biogen idec

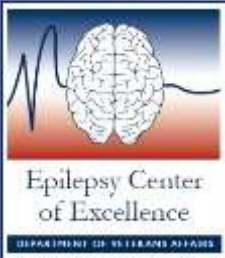


THE EPILEPSY COMPANY™



PatientsLikeMe and the VA

- **Policy for Optimal Epilepsy Management (P.O.E.M.)**



- Validate the patient-reported benefits of using the PatientsLikeMe platform in an observational study
 - Next generation of the 2009-2011 UCB-PatientsLikeMe Epilepsy Partnership
 - Epilepsy Centers of Excellence (ECoE) as a third party expert to observe the impact of use of the PatientsLikeMe platform in patient activation and literacy

- **WarriorsLikeMe**



- Longitudinal cohort research to examine the effect of ten years of conflict on warfighters
 - Unsolicited response to remarks by Assistant Secretary of Defense (Health Affairs) & Director of TRICARE Management Activity Dr. Jonathan Woodson
 - Focus on TBI, Mental Health, Substance Abuse and Addiction, Major Limb Injury and Amputation, Vision/Hearing Impairment

Before there was P.O.E.M...

PatientsLikeMe and UCB partnered to develop the premier online epilepsy community, and to date have discovered together compelling patient-reported benefits of using the platform.

One-third of respondents had no one in “the real world” with whom to discuss their epilepsy. After joining PatientsLikeMe, two-thirds reported a connection to at least one other person with epilepsy.

59% -the site has given me a better understanding of my seizures

50% - PatientsLikeMe helped me understand side effects

30% - PatientsLikeMe helped me be more adherent

28% - PatientsLikeMe gave me more and better control over my condition

49% - recording my seizures helps me manage my condition

21% - Because of the site I insisted on seeing a specialist

23% - I have had fewer visits to the ER

27% - PatientsLikeMe helped me find ways to reduce side effects

**Published in *Epilepsy & Behavior*
Presented at AAN 2011
N = 221 survey respondents**

P.O.E.M. Goes a Step Further



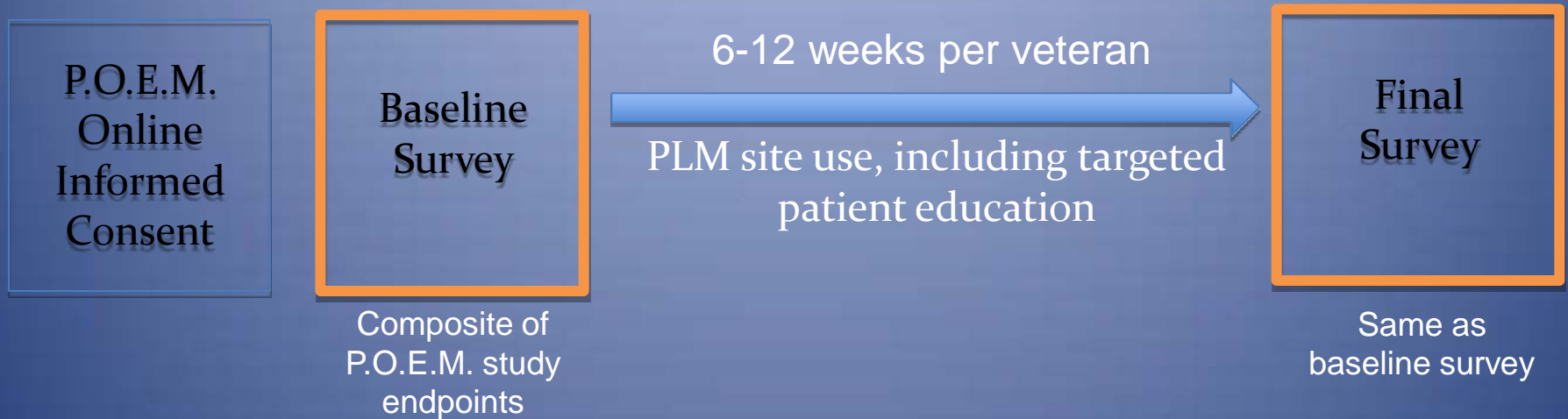
*Principal Investigator John D.
Hixson, MD
San Francisco VA ECoE , UCSF*

Objective: Empirically observe impact of the use of the PatientsLikeMe platform on veteran-reported outcomes in epilepsy

- Summer 2012 pilot ongoing in SF ECoE to finalize endpoints
- Full study launch expected Fall 2012
- Desired end state: Publication, exhibition, recommendation of new standards of care in epilepsy

P.O.E.M. is made possible by a research grant from UCB Inc.

P.O.E.M. Study Overview



Candidate Study Endpoints

- Epilepsy Self-Efficacy Scale (ESES)
- Modified Medication Adherence Scale
- Epilepsy Self-Management Scale (ESMS)
- Personal Resource Questionnaire 85 (PRQ85)
- Interpersonal Support Evaluation List (ISEL)
- Jacoby Stigma Scale (3 item)
- EQ5-D (QoL utility measure)
- PAM (Patient Activation Measure)
- QOLIE-10 and/or 31
- Liverpool Seizure Severity Scale

WarriorsLikeMe

In May 2012 PatientsLikeMe proposed to augment and customize elements of our current platform to create an online community on behalf of the Military Health System (MHS), serving six major categories of injured warfighter:

- **Traumatic Brain Injury (TBI)**
- **Psychological Injury (esp PTSD)**
- **Alcohol and Substance Abuse**
- **Major Limb Injury or Amputation**
- **Vision Impairment**
- **Hearing Impairment**

Tasks:

1. Assess warfighter-specific needs and create credentialed, secure entry portal
2. Create communities for target conditions, including disease-specific PRO scales
3. Assessment by user survey and preliminary data delivery
4. Refinement and redesign of communities
5. Integration with MHS systems and additional data delivery

Proposed timeline: Four Years Commencing 2013

Long-Term Ambulatory EEG Monitoring of Veterans and Military Personnel with TBI: A Clinical Study Opportunity

Doug Sheffield VMD, PhD
VP Clinical Research, NeuroVista

Kent Leyde, MSEE
Chief Technical Officer, NeuroVista

Conflict of Interest Disclosure

- I have the following disclosures related to the presentation
 - I am an employee of NeuroVista Corporation

NeuroVista



- Located in Seattle, Washington
- Focused on developing technologies for the management and treatment of epilepsy
- Unique EEG platform technologies with multiple value propositions
- Proven team with unique domain expertise
- Presently conducting first-in-man study in Australia

Unmet Need

- Identifying markers for TBI patients who will develop epilepsy
- Preventing epilepsy in “at risk” TBI patients
- Intervening at the earliest evidence of sub-clinical seizures or epileptiform activity
- Manage epilepsy aggressively based on quantitative EEG data to minimize its impact

Proposed Solution

- Collect long-term EEG data from TBI patients
- Collaborate with the VA ECoE to design a Long-Term EEG Monitoring Clinical Study of Veterans/Military Personnel with TBI
 - Monitor TBI patients to identify who develops epilepsy
 - Determine if there are EEG markers of epileptogenesis in the TBI patients
 - Track cognitive performance via event related potentials
 - Provide early intervention based on sub-clinical seizures or abnormal EEG
 - Manage therapy based on electrographically identified seizures
- Provide regular clinical/patient reports that summarize EEG findings

Proposed EEG Monitoring System

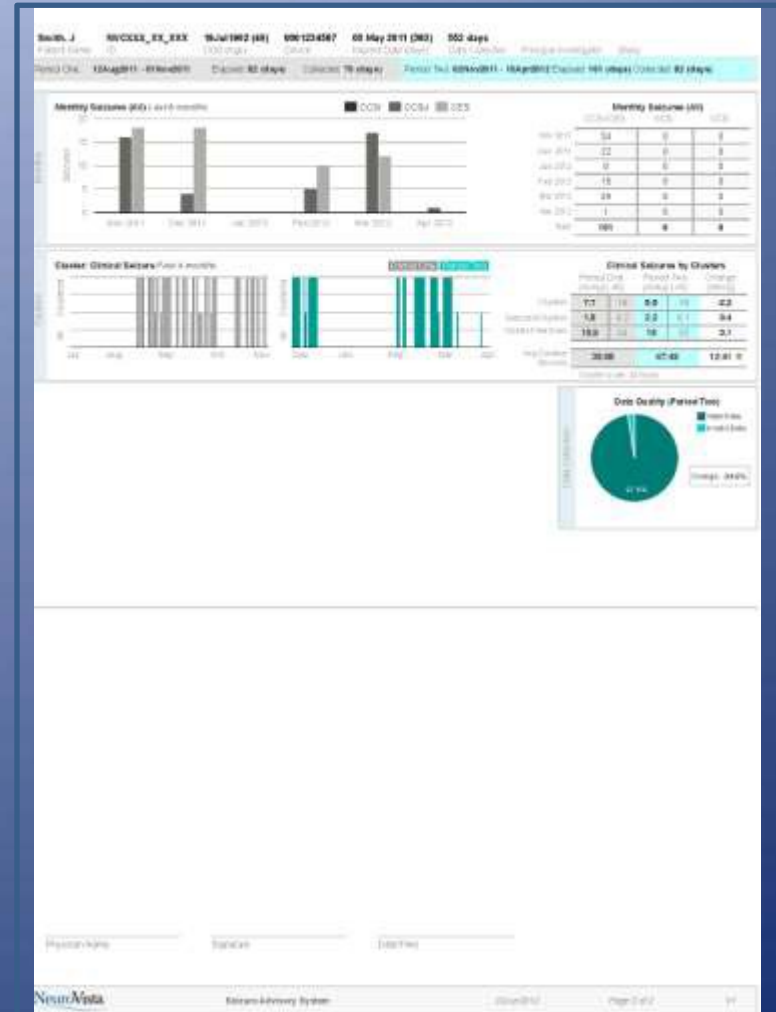
- Continuous EEG monitoring device
- Sub-galeal implant
 - Minimally intrusive
- Periodic data retrieval and recharge
 - Data automatically transmitted to central location; VA neurologist logs in for review
- Rich set of analysis tools automatically annotates and characterizes data
- Entirely reversible



Proposed Clinician/Patient Reporting Portal

- Includes a secured HIPAA compliant environment for patients to view their own quantitative data on-line in real time.
- Provides clinicians with a secured cloud hosted system to quantify and present information for use in patient care.
- Ability for clinicians to assemble customized clinical reports tailored to each patient which includes:
 - Summary of EEG findings comparing data over different time intervals
 - Device maintenance compliance
 - Summary of cognitive performance
 - Medication compliance

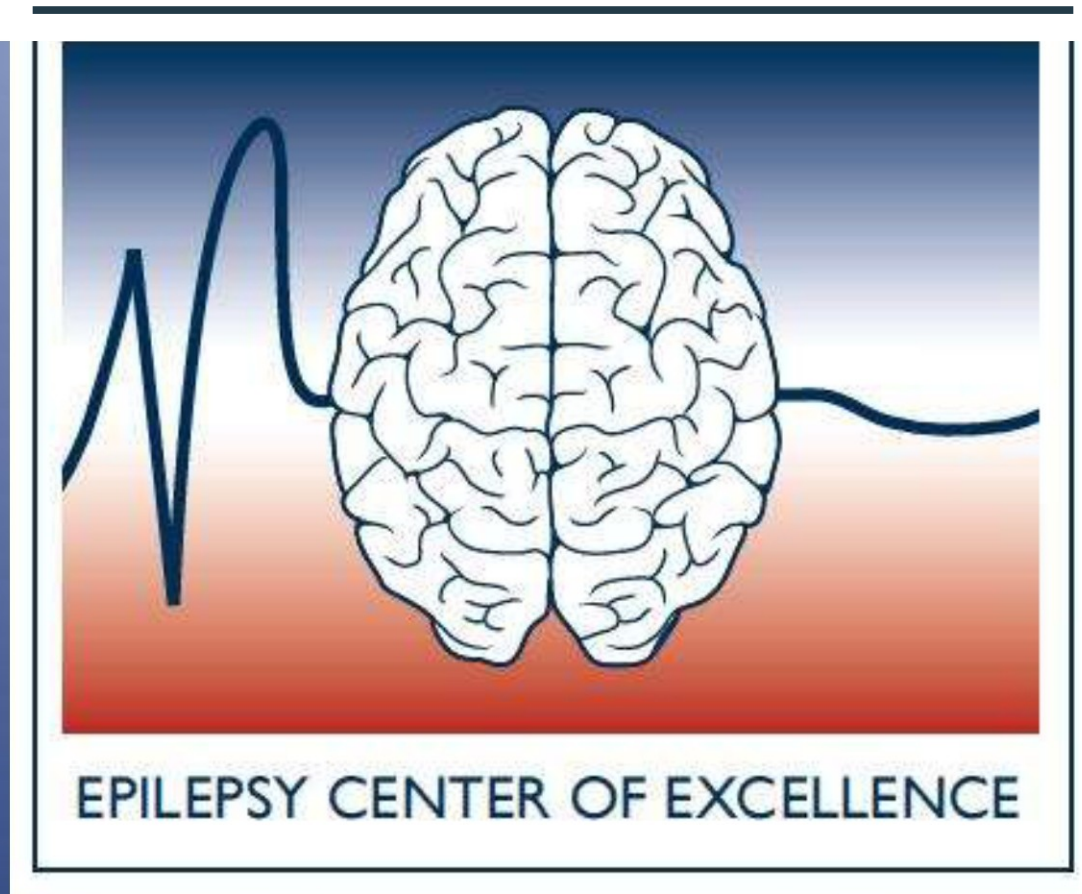
Sample Clinical Report



Next Steps

- Collaborate with VA ECoE to develop a clinical study proposal
 - Form a clinical study planning group to develop a clinical study plan/schedule/budget
 - Who else should participate?
- Develop extensions to NeuroVista system to support TBI study objectives
 - Quantify epileptogenic activity
 - Develop P300 cognitive assessment capabilities
 - Specialized reports for TBI management
- Explore integrating patient report portals with PLM/WLM

Questions/Discussion



www.epilepsy.va.gov

