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TITLE: Phenotypes of Comorbidity in Epilepsy: Variation by TBI Severity and Deployment Status

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CONTRACTING ORGANIZATION: Western Institute for Biomedical Research
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14. ABSTRACT

The proposed study will leverage data from an existing Department of Defense (DoD) funded Post-traumatic epilepsy study(W81XWH-16-2-0046) that is examining the relationship between mild traumatic brain injury (mTBI) and epilepsy in deployed Post-9/11 Veterans. We will add to that study by identifying patterns of comorbidity in Post-9/11 deployed Veterans with epilepsy using latent class analysis, and by adding a cohort of non-deployed Post-9/11 Veterans who are also in VA care for the same analysis. As a result, with a small investment we will be able to identify specific phenotypes of comorbidity in Veterans with epilepsy and be able to determine if those patterns are different for individuals who 1) were deployed, where the likelihood of blast exposure is higher, and 2) have TBI exposure compared to those who do not. Finally, we will examine the extent to which these comorbidity phenotypes help explain premature death, and the specific cause of death in these individuals with epilepsy. These findings will have enormous implications for health care delivery for Veterans and Active Duty Service Members with epilepsy. For instance, the data may suggest that chronic disease is an important cause of death. This finding would suggest the importance of care coordination between primary care providers and neurologists/epileptologists providing subspecialty care for patients with epilepsy. In addition, data from this study can be used as a foundation to identify genetic markers that are associated with distinct epilepsy comorbidity phenotypes. We have compiled VA and DoD data for the deployed and non-deployed cohort. We have developed an epilepsy identification algorithm and we will perform chart abstraction to evaluate the algorithm.

15. SUBJECT TERMS
Epilepsy; comorbidity; multimorbidity; military deployment; traumatic brain injury

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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Unclassified	Unclassified	Unclassified	Unclassified	11	**19b. TELEPHONE NUMBER** *(include area code)*

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1. INTRODUCTION

The literature indicates that epilepsy is a chronic condition that, in combination with its comorbidities, has a profound impact on patients, their families, society, and health care systems. Moreover, data suggests a bi-directional relationship between epilepsy and a number of mental health comorbidities, and emerging data suggests bidirectional relationships with other conditions (i.e.,neuro-immunological conditions, dementia, obstructive sleep apnea). Recommendations for longitudinal research including epilepsy and comorbidity by the IOM are particularly salient for the current cohort of combat service members and veterans, due the high rates of mental health and other comorbidities thought to have a bidirectional relationship with epilepsy. Understanding the natural history of comorbidity in a military/veteran cohort in conjunction with advanced statistical models provide a unique opportunity to determine if 1) there are clinically meaningful comorbidity phenotypes in people with epilepsy 2) comorbidity phenotypes in epilepsy vary by deployment and TBI status, and 3) comorbidity phenotypes reliably predict mortality/SUDEP or disease-specific mortality. We are currently in process of analyzing and cleaning DoD data from DaVINCI.

2. KEYWORDS:

Epilepsy, mild traumatic brain injury, epidemiology, comorbidity, mental health, neurodegeneration.

3. ACCOMPLISHMENTS:

Major Tasks

- **Major Task 1:** Complete Regulatory Requirements for Study
  Anticipated completion: Month 6
  Actual completion: Month 9: Jun-2019

- **Major Task 2**: Identify cohort who meet criteria
  Anticipated completion: Month 6 (100% complete)
  Actual completion: N/A; VA and DoD data was received in April 2020.

- **Major Task 3:** Create comorbidity phenotypes using latent class analysis
  Anticipated completion: Month 30 (35% complete)
  Actual completion: N/A;

- **Major Task 4:** Conduct survey to assess lifetime TBI exposure
- **Anticipated Completion:** Month 30
  Actual completion: N/A

- **Major Task 5:** Identify adverse outcomes and conduct analysis by phenotype
  Anticipated completion: Month 32
  Actual completion: N/A

- **Major Task 6:** Complete manuscripts
  Anticipated completion: Month 36
  Actual completion: N/A

Accomplishments During This Reporting Period

- **Major Task 1: Complete Regulatory Requirements for Study**

We received IRB approval for a continuing review with amendment on October 9th, 2020 with an expiration of October 8th, 2021. The amendment includes 1) changes to study staff; 2) some clarifications related to prior amendments; 3) addition of a small chart abstraction to evaluate epilepsy identification algorithm; 4) Changing data sources and analysis procedures to include the use of psychogenic non-epileptic seizure (PNES) cohort data that was recently added to the CHOP repository, US VETS to identify deployment status, and VA Homelessness registry to identify homelessness in the cohort; and 5) changing the location of the latent class analysis to VINCI . We submitted the continuing review with an amendment to HRPO on October 14, 2020 and received a communication on October 23, 2020 that it was approved.

- **Major Task 2: Identify cohort who meet criteria**

We have continued team meetings to develop the list of conditions we will include in models. We have identified our cohort for the study using VA and DoD health system data. We are enhancing our ability to identify valid cases of epilepsy using new algorithms that can be implemented in any EHR by comparing different approaches to our gold standard cases which have been validated using chart abstraction. We have also begun analyses examining risk for epilepsy by TBI status among individuals who have been deployed and not deployed. We completed a review of the literature to determine if new adaptation to the epilepsy identification algorithm are needed and to incorporate ICD10 codes.

We identified epilepsy in the cohort of individuals who entered VA care before the end of 2014 to ensure accurate ascertainment of deployment status. We selected those with two years of VA care before the end of FY19, had at least one year of care in DoD, and whose age was 17 or greater at first VA care. From this cohort of 1,245,648, we identified 30,993 who met criteria for epilepsy:
1. Epilepsy specific diagnosis code and antiseizure medication
2. >1 Convulsion/seizure diagnosis code and antiseizure medication
3. 1 Convulsion/seizure diagnosis code and service connected disability for seizure, or identification as confirmed epilepsy in Dr. Altalib's psychogenic non-epileptic seizure (PNES) cohort (N=864).

There were 102 individuals with epilepsy in the PNES cohort and 100% of these individuals were identified as epilepsy positive by our algorithm.

After identifying putative epilepsy and no epilepsy cohorts, we excluded individuals who had seizure diagnoses but did not meet epilepsy criteria (n=19,368)

Table 1 provides descriptive characteristic of those that, based on our current evaluation, have putative epilepsy N=30,993 (2.53% of total cohort) and those that do not have epilepsy N=1,195,287 (97.47% of total cohort). All bivariate statistics examined using the chi square statistic were statistically significant p<.0001.

Table 1. Demographic Characteristics for Post-9/11 Veterans with Epilepsy vs. No Epilepsy using

	Epilepsy N=30,993	**No Epilepsy n=1,226,280**
	% (N)	**% (N)**
TOTAL:	2.53 (30,993)	97.47 (1,195,287)
DEMOGRAPHICS:		
Age:		
11-16	0.09 (27)	0.02 (182)
17-29	39.89 (12362)	42.21(504504)
30-39	31.08 (9633)	28.05 (335336)
40-49	17.60 (5455)	20.81 (248706)
50 and older	11.34 (3516)	8.91 (106559)
Sex: Female	20.64 (6398)	16.90 (202001)
Race/Ethnicity:		
White	67.51 (20924)	59.57 (711973)
African American	16.87 (5229)	18.21 (217707)
Hispanic	8.08 (2505)	9.96 (119015)
Asian	1.29 (400)	2.44 (2.44)
Native American/Pacific Islander	1.99 (618)	1.80 (21517)
Unknown	4.25 (1317)	8.03 (95931)
Marital Status: Married	50.18 (15552)	48.83 (583698)
MILITARY CHARACTERISTICS:		
Deployment Status: Deployed	60.44 (18732)	70.14 (838424)
Branch:		
Army	56.40 (17480)	52.83 (631523)
Marines	12.88 (3991)	14.71 (175823)
Navy/Coast Guard	15.85 (4913)	17.31 (206880)
Air Force	14.63 (4533)	14.88 (177878)
Other/Unknown	0.25 (76)	0.27 (3183)
Component:		
Active	78.77 (24412)	67.91 (811694)
Guard	11.12 (3447)	16.50 (197182)
Reserve	6.09 (1887)	9.64 (115193)
Unknown	4.02 (1247)	5.96 (71218)

These data suggest that before the index date the putative epilepsy cohort (hereafter **epilepsy cohort**) is older, more likely to be female, more likely to be white, less likely to include Veterans who served in the Marines, Navy or Coast Guard, and more likely to include those who served most recently on Active Duty (vs. deployed National Guard/Reserve). The individuals who had an index date prior to the age of 17 were likely diagnosed with or seizures/medications as dependent children of military personnel.

We recently received the National Death Index data which includes cause of death for this cohort.

Table 2. Comorbidities Diagnosed Before Index Date by Epilepsy Status

COMORBID CONDITIONS:	Epilepsy N=**30,993**	No Epilepsy n=**1,226,280**
Any TBI	37.86 (11735)	14.82 (177165)
Initial Screen Positive, no evidence	1.34 (415)	1.88 (22467)
mTBI	21.38 (6626)	9.74 (116418)
Moderate/Severe TBI	9.03 (2798)	1.85 (22079)
Penetrating TBI	3.54 (1097)	0.28 (3367)
Unclassified/other TBI	2.58 (799)	1.07 (12834)
Depression	51.89 (16081)	25.26 (301929)
Substance Use Disorder (any)	41.38 (12824)	22.27 (266210)
Opioid	9.46 (2931)	1.78 (21224)
Alcohol	29.50 (9142)	15.14 (180920)
Amphetamine	2.71 (840)	0.65 (7782)
Cannabis	8.61 (2670)	3.46 (41371)
Sedative	3.71 (1149)	0.49 (5892)
Cocaine	4.69 (1453)	1.37 (16320)
Hallucinogens	0.48 (148)	0.15 (1775)
Other Drug Abuse	21.70 (6727)	10.47 (125135)
Posttraumatic Stress Disorder	41.61 (12897)	20.80 (248651)
Anxiety	43.11 (13361)	18.70 (223503)
Bipolar Disorder	16.69 (5174)	4.87 (58229)
Schizophrenia	1.87 (581)	0.63 (7530)
Hearing loss / Tinnitus	19.91 (6170)	14.11 (168611)
Vestibular Dysfunction	2.30 (714)	0.60 (7172)
Dizziness	15.98 (4954)	3.77 (45027)
Photophobia, Blindness or Blurred Vision	5.39 (1669)	1.52 (18198)
Cognitive Dysfunction (dementia/MCI diagnoses)	4.29 (1329)	0.50 (5962)
“memory loss” diagnosis	10.26 (3181)	1.98 (23668)
Stroke/ Transient Ischemic Attack	13.52 (4190)	1.49 (17787)
Cardiovascular conditions	17.61 (5458)	4.76 (56891)
Hypertension	29.97 (9288)	17.70 (211544)
Diabetes	6.71 (2080)	3.13 (37363)
Headache	52.78 (16357)	19.85 (237262)
Neck or Back Pain	62.49 (19367)	47.75 (570723)
Other Pain (arthritis /musculoskeletal/ comprehensive)	61.50 (19061)	47.75 (570731)
Obesity	21.63 (6703)	17.68 (211312)
Smoker Ever	65.24 (20219)	46.61 (557066)
Obstructive Sleep Apnea	15.56 (4822)	7.65 (91382)
Insomnia	34.68 (10748)	14.86 (177602)
Hypersomnia	7.53 (2334)	3.91 (46728)
Amputation	0.85 (262)	0.36 (4255)
Spinal cord injury	1.76 (545)	0.43 (5158)
Burn	3.31 (1025)	1.81 (2163)
ADVERSE EVENTS:		
Suicide Related Behavior	13.96 (4328)	3.94 (47097)
Overdose	17.06 (5287)	4.29 (51268)
Homelessness (VA data only)	10.45 (3238)	3.84 (45904)
Mortality as of April 30, 2020	7.63 (2365)	1.83 (21888)

Due to the large cohorts all comparisons using the chi-square statistic were significant p<.0001.Those with epilepsy were more likely to have had any type of TBI, substance use disorder, smoking history, and chronic disease prior to index day compared to the no epilepsy cohort. Those in the **no epilepsy cohort** were less likely to have mental health conditions and cognitive dysfunction prior to the index date, and were more likely to have been deployed than those with epilepsy. Those with epilepsy were also significantly more likely to have adverse events of overdose and suicide related behavior prior to the index date, and more likely to experience homelessness while in VA care and mortality before April 30,2020.

- **Major Task 3: Create comorbidity phenotypes using latent class analysis**
  We have identified the conditions in VA and DoD data.

  Drs. Pugh and Altalib (co-investigator) are conducting social network analysis of symptoms for individuals included in the VA comprehensive TBI evaluation as a possible example of a "phenotyping" approach. Data are still forthcoming due to software issues.

  We have identified all conditions of interest for LCA in both DoD and VA. LCA analysis will begin during FY21 Q1.

Opportunities for Training and Personal Development

Nothing to report.

Dissemination to Communities of Interest
Nothing to report

Plans for Next Reporting Period
[1] Major Task 1: We will update IRB and HRPO as needed.

[2] Major Task 2: We will finalize our evaluation of the epilepsy cohort algorithm. As part of validation of any changes we believe are needed based on findings we will validate a limited number of cases using the VA electronic medical record access platform, CAPRI, and adding documented, probable and possible PNES cases from our prior studies to develop positive predicted values. We will examine the associations between epilepsy and TBI severity and deployment status in more detail.

[3] Major Task 3: We will conduct further descriptive analyses to compare comorbidity before and after index date by deployment and TBI severity status, and develop several manuscripts in the next quarter. The first will describe predictors of epilepsy in this cohort with an emphasis on deployment status and TBI severity. The second will describe predictors of mortality in this cohort with an emphasis on epilepsy status, deployment status and TBI severity. We will also begin to process the National Death Index data to better understand cause of death from sudden unexpected death in epilepsy (SUDEP), chronic disease, accidents, deaths of despair etc.We anticipate that the latent class analysis will begin in Q2 of FY21.

4. IMPACT

Impact On The Development Of The Principal Disciplines Of The Project

None to date. Our algorithm evaluation will be broadly distributed and incorporate leaders in the field.

Impact On Other Disciplines
Nothing to report

Impact On Technology Transfer
Nothing to report

Impact On Society Beyond Science And Technology
Our stakeholder outreach will continue, providing community education opportunities. We are developing a more formal relationship with the Epilepsy Foundation in Utah, expanding our web presence to a webpage on the University of Utah and social media.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change:

Due to the high numbers for prevalence of epilepsy, we will evaluate the veracity of the epilepsy algorithm due to changes in medication use patterns in VA, DoD and civilian society. Now that we have IRB and HRPO approval we can conduct a limited chart abstraction to assess the existing algorithm and possible changes that will be needed to exclude individuals who have seizures (e.g., alcohol withdrawal, drug exposure (e.g., tramadol), or other biological/psychological non-epileptic seizures. This will provide a much-needed update to epidemiological methods that will include leaders in the field, and will guide future population-based studies such as this.

Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to report.

Changes that had a significant impact on expenditures
Due to delays in start-up we have accordingly limited our spending to ensure that we have appropriate funding available to process the data, conduct phenotype analyses and distribute surveys.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.
No changes to report. This study does not have face to face contact or lab measures that have been ceased for the COVID-19.

6. PRODUCTS

Conference Papers and Presentations
We have begun development of a research program website that participants can view that includes study information, frequently asked questions, and informational links.

https://medicine.utah.edu/internalmedicine/epidemiology/research_programs/torch/

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

Organization Name:	Location of Organization:	Organization Contributions:
Western Institute for Biomedical Research (WIBR)	Salt Lake City, Utah	Collaboration & Facilities

Name:	Project Role:	Researcher Identifier (ORCID):	Percent Effort:	Person Month(s) Worked:
Mary Jo Pugh	Principal Investigator	0000-0003-4196-7763	12%	1.5
Jacob Kean	Co-Investigator	0000-0002-8577-0586	10%	1.2
Amy Henion	Research Analyst		25%	3
Eamonn Kennedy	Research Scientist		25%	3

Organization Name:	Location of Organization:	Organization Contributions:
UT Health San Antonio	San Antonio, TX	Collaboration

Chen-Pin Wang	Biostatistician		20%	2.4

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
The following grant applications were funded with DoD with anticipated funding at the end of September, 2020.
Post-Traumatic Epilepsy: Cognitive and Neuro-Behavioral Characteristics (PTE-CNBC) among Post-9/11 United States war Veterans (PI: Mayo; 5% effort)
Military Injuries: Understanding post-Traumatic Epilepsy [MINUTE], Health and Quality of Life Effects of Caregiving (PI: Pugh; 5% effort)
Frontotemporal Dementia: Military Exposures and Disease Characteristics (FTD-MEDIC) (PI: Mayo; 2.5% effort)
FITBIR: Accelerating Synthesis of TBI Research Using Novel Methods (FAST RUN Methods) (PI: O'Neil; 5% effort)
Sex Difference in Cognitive and Mental Health Functioning Following Mild Traumatic Brain Injury (PI: Jak; Consultant)

The following grants have ended or are in process of requesting no cost extension (NCE) with significantly reduced effort:
Ended before September 2020
Healthcare Utilization Patterns and Associated Costs for Gulf War I Era Veterans (Ended March 2020; 10% effort)
The UCD-DGMC TBI Neutral Network- Precision Medicine Paradigm for Complex Trauma (End September 30 2020; 10% effort)

End September 2020: Requested NCE
Epidemiological Characterization and Prognostic Models for PTE: A Collaborative TBI-MS and VHA Study. (2.5% effort)
Post-Traumatic Psychogenic Seizure and Epilepsy Project (2.5% effort)
Factors Associated with Outcomes in Patients with Vestibular symptoms Related to Traumatic Brain Injury (2.5% effort)
The Epidemiology of Epilepsy and Traumatic Brain Injury: Severity, Mechanism, and Outcomes (2.5%)

Pugh Total funded effort for FY21: 85%

What other organizations were involved as partners? Nothing official to report. Working on relationship with Utah Epilepsy Foundation.

8. SPECIAL REPORTING REQUIREMENTS

[1] Quad Chart Attached

Phenotypes of comorbidity in epilepsy: Variation by TBI severity and deployment status

W81XWH-17-ERP-IDA

PI: Pugh M.J. **Org:** Western Institute for Biomedical Research **Award Amount: $567,672**

Study/Product Aim(s)

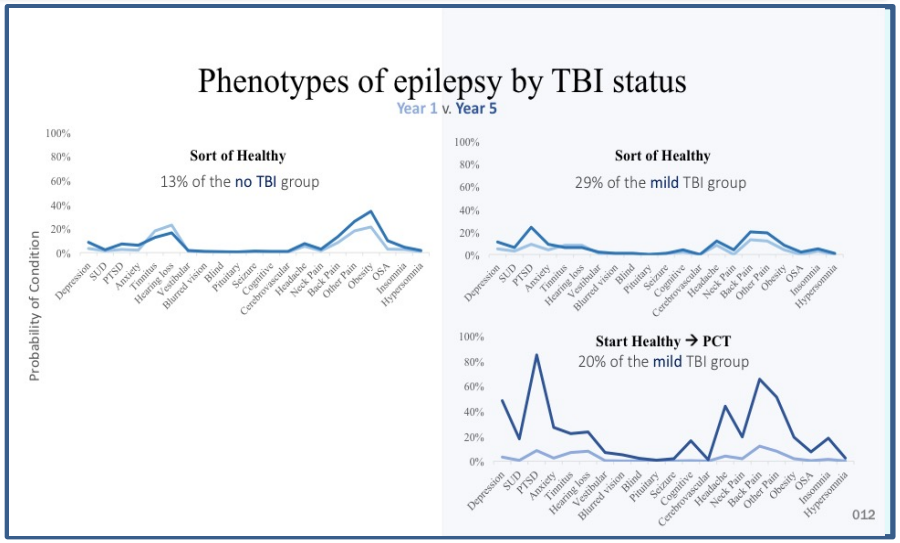
Aim 1: Identify neurological, psychological, and chronic disease comorbidity for a cohort of Post-9/11 Era Veterans with epilepsy who received VA care during at least two years (2002-2017) and determine if there are significant differences in comorbidity before and after identified epilepsy by TBI status (yes/no), TBI severity, Post-9/11 deployment status (previously deployed/not deployed).

Aim 2: Describe longitudinal phenotypes of comorbidity for Veterans with epilepsy and determine if phenotypes vary by TBI and deployment status.

Aim 3: Identify variation in adverse outcomes by comorbidity phenotypes adjusting for socio-/military demographic characteristics.

Approach

This observational cohort study will use VA and DoD data to identify comorbidity phenotypes among deployed and non-deployed Veterans with epilepsy using latent class analysis. It will also identify variation in phenotypes by TBI status and examine variation in adverse outcomes by phenotype.



Timeline and Cost

Activities / CY	19	20	21
Phase I: Regulatory and Administrative data compilation			
Phase 2: ID comorbidity phenotypes by deployment status (Aims 1-2)			
Phase 3: Outcomes analysis by phenotype (Aim 3)			
Estimated Budget (500K)	**$166**	**$204**	**$202**

Updated: 07/29/2020

Goals/Milestones

CY19 Goal –

X Regulatory approvals

X Data acquisition

X Identify non-deployed cohort and prevalence of comorbidity. (Aim 1)

CY20 Goal –

☐Identify phenotypes of comorbidity by deployment status (40% complete)

☐Determine if trajectories are significantly different by deployment and TBI status (Aim 2)

CY21 Goal –

☐Conduct analyses of adverse outcomes by phenotype (Aim 3)

☐Conduct small survey

Comments/Challenges/Issues/Concerns

- Received DaVINCI data this quarter and have used to identify epilepsy and comorbidities.

Budget Expenditure to Date

Projected Expenditure: $370,511

Actual Expenditure: $190,847