AWARD NUMBER: W81XWH-17-1-0649

TITLE: Post-Traumatic Psychogenic Seizure and Epilepsy Project

PRINCIPAL INVESTIGATOR: Hamada Hamid Altalib

CONTRACTING ORGANIZATION: VA Connecticut Research and Education
West Haven, CT 06516-2770

REPORT DATE: October 2020

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution is unlimited

.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2020	Annual	30 Sept 2019 - 29 Sept 2020

4. TITLE AND SUBTITLE

Post-Traumatic Psychogenic Seizure and Epilepsy Project

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-17-1-0649

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT:

Over 80,000 veterans who utilize the VA healthcare system are diagnosed with epilepsy, and preliminary data suggest a substantial proportion actually suffer from Psychogenic Non-Epileptic Seizures (PNES) instead, a psychiatric disorder. In the DSM-V, PNES is classified as a conversion disorder, a type of somatic symptom disorder diagnosed as such after appropriate medical assessment finds the presenting neurological symptoms incompatible with neurological pathophysiology. In this case, individuals with PNES display seizure-like events without a vEEG correlate and can exhibit characteristic semiology distinct from epileptic seizures. Known risk factors for developing PNES in the general population include mental, physical, and social distress. Among veterans, a history of post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI) are associated with PNES; however, the complex relationship between these three disorders is not well understood.
The main objective of this study is to establish the role of PTSD, TBI, and other co-morbidities (chronic pain, military sexual trauma, female gender) in the causal pathway of PNES among post-9/11 veterans. Secondary objectives are to study the relationship between the treatment (psychotropic and psychotherapeutic) of PTSD, mood, and other anxiety disorders and the risk of developing PNES, the severity of the disorder (number of monthly psychogenic seizures), and likelihood of recovery (seizure-free for six months). **CONTINUED ON NEXT PAGE**

15. SUBJECT TERMS

None Listed

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	28	19b. TELEPHONE NUMBER *(include area code)*

14. ABSTRACT: CONTINUED FOR W81XWH-17-1-0649 ANNUAL OCTOBER 2020

This is a longitudinal retrospective cohort study of veterans who utilized the VA healthcare system for at least two years during the period of 2002-2015. We have grouped them into those who meet criteria for epilepsy (n = 6811), PNES (n = 327; as defined by the International League Against Epilepsy), and a comparison group (n = 1.2 million) who have no documented epilepsy or PNES history. The cohort was constructed from existing VA electronic and administrative sources utilizing validated algorithms to identify Veterans with epilepsy as well as co-morbid medical and psychiatric disorders. The data will be uploaded into a VA SQL Server database for secure storage, query and manipulation of subject data. Patient data has been de-identified to protect confidentiality.

During primary analysis, Generalized Estimating Equations (GEE) will be used to determine if the rate of change in newly diagnosed PNES increases over time and specifically, if TBI identified in DoD/VA is significantly associated with that change. During secondary analysis, we will estimate the number of newly diagnosed Veterans and prevalence rates of PNES using Poisson regression. Other statistical analysis methods include two logistic regressions; and time-to-event models to examine how pharmacologic treatments for PTSD (or comorbid depression or anxiety) are negatively associated with PNES development.

We hope the results of this study influence clinical management of veterans with PNES, that by clearly identifying comprehensive risk factors, elucidating a causal pathway, and evaluating the timing and type of mental health treatment may improve the health of this vulnerable population as well as decrease healthcare costs.

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

PNES is a dissociative disorder that is a major burden on veterans. Over 80,000 veterans who utilize the VA healthcare system currently carry the diagnosis of epilepsy, and preliminary data suggest a substantial proportion of those may have PNES instead. Similar to focal seizures with change of consciousness or generalized tonic-clonic seizures, people who suffer from PNES and other dissociative disorders lose partial or complete integration of perception and are disconnected from their environment during the events. According to the VA's Epilepsy Centers of Excellence (ECOE) 2012 Annual Report, PNES accounted for 29% of all inpatient epilepsy monitoring unit (EMU) evaluations within the national ECOE network, nearly identical to rates reported in civilian populations. Estimated direct health costs saved per patient identified per year is $13,750, which extrapolates to 2.6 million dollars in cost savings per year to the VA system from corrected diagnoses. Veterans with PNES may suffer worse outcomes than civilians with PNES. For instance, the delay in the diagnoses of PNES from their first seizure is five years in Veterans compared to only one year in civilians, which may impact their employment, social function, and ability to drive and access resources. Furthermore, veterans with PNES are treated with anti-epileptic drugs (AED) four times more often than civilians with PNES, exposing them to the risk of side effects and costs of unnecessary medications.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Psychogenic non-epileptic seizures, Traumatic brain injury, Post-Traumatic Stress Disorder, Video EEG, conversion disorders, functional neurological disorders, Anti-seizure drug, epilepsy

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aim 1: **Describe the change in prevalence of newly diagnosed Veterans with post-traumatic and non-traumatic Psychogenic Non-Epileptic Seizures (PNES) in the VA Post 9/11 population over time**

Specific Aim 2: **Describe the risk factors (Female gender, PTSD, Depression, Anxiety, Military Sexual Trauma, Chronic Pain, TBI) for PNES including PNES subsequent to TBI (PTPNES)**

Specific Aim 3: **Explore whether prior psychotropic and psychotherapeutic treatments for mood and anxiety disorders decrease the risk of developing PNES.**

Specific Aim 3a (Exploratory): **Explore whether prior psychotropic and psychotherapeutic treatments for mood and anxiety disorders decrease the severity of PNES (number of monthly psychogenic seizures) and increase the likelihood of recovery (seizure-free for six months).**

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting

Major Task 1: Complete Regulatory Requirements for Study	Months	Complete
Coordinate with Sites for MOU/ DTA completion, nondisclosure agreements	1-2	x
Finalize protocol chart abstraction tool	PTF	x
Secondary site IRB protocol submission (expedited)	1-4	
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	1-6	x
Submit amendments, adverse events and protocol deviations as needed	1-36	x
Coordinate with Sites for annual IRB report for continuing review	Annually	x
Milestone Achieved: Local IRB and HRPO approval at VACT, SLC VA	3-6	x
Major Task 2: Identify cohort who meet criteria for epilepsy and PNES		
Complete data request documentation for VA and DoD data sources	PTF	x
Obtain VA and DOD data, identify TBI severity, comorbidity, and other clinical characteristics	6-12	x
Milestone Achieved: Raw Data obtained	12	x
Subtask 2:Identify epilepsy in FY02-FY15 cohort	13	x
Compile data from VA and DoD data sources and identify epilepsy and PNES characteristics	13	x
Milestone Achieved: Cohort of Veterans of Epilepsy identified	13	
Conduct/interpretation of logistic regression analyses on Post-9/11 VA cohort and complete manuscripts	14-18	Pending
Milestone Achieved: Aims 1 and 2 completed	18	
Major Task 3: Identify Sample for Aim 3		
*Identify sampling frame for people at risk for PNES (for chart abstraction)	19	x
Major Task 3: Identify Sample for Aim 3	20-26	
*Identify sampling frame for people at risk for PNES (for chart abstraction)	19	x
Conduct medical chart abstraction for PNES validation and identify sampling frame to identify PNES and confirmed epilepsy cases from epilepsy cohort		
Milestone Achieved: Study sample frame for Aim 3 identified	27	x

Major Task 4: Conduct analysis for Aim 3	32-36	
Conduct interim and final analyses/ interpretation for Aims 3	28-32	
Complete manuscripts for publication	32-36	
Milestone Achieved: Report findings of the impact of mental health treatment on the incidence and severity of PNES (Aim 3)	36	

We submitted an abstract on the higher than expected rates of psychosis NOS coded in epilepsy and PNES patients, in which 31% of PNES patients and 28% of epilepsy patients were coded for psychosis NOS, to the American Academy of Neurology. Further research will investigate the source of this finding to determine whether this is due to EHR coding error, due to peri- or post-ictal phenomena, or co-morbid psychosis. That was accepted to the American Academy of Neurology April 14, 2020.

We submitted a manuscript describing the increased rate of suicide associated with epilepsy. This has previously been described, but no studies have reported the rates of suicide and suicide related behavior (SRB) associated with psychogenic non-epileptic seizures (PNES).

Chi-square tests were used to examine bivariate relationships between categorical variables and t-tests or nonparametric tests, as appropriate, were used for continuous variables. Because our study is a cohort study and the primary outcomes were rare events over time, we used Poisson regression with a log link and robust variance estimates to calculate relative rates of suicide and suicide related behavior (RR) and 95% confidence intervals (CI).

A major component of our research is to link Department of Defense (DoD) data sources to VA data with Mary Jo Pugh, the primary investigator who is leading the DoD collection, integration, and analysis. We have established a data sharing agreement to link of DoD and VA data and are waiting for permissions to be granted from VA Informatics and Computing Infrastructure (VINCI), the platform through which data will be shared.

What opportunities for training and professional development has the project provided?

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Yarden Bornovski has had the opportunity to take Coursera courses in basic research methods and the use of statistical programs such as SPSS and R. Ebony Jackson Shaheed has participated in multiple remote statistical design clinics at the Yale Center for Analytical Sciences. Ebony Jackson Shaheed has also had the opportunity to take courses from Coursera and Udemy academy for Bayesian statistics.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."
Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We intend to continue to analyze the data and risk factors on the Veterans identified with PNES. We intend to use natural language processing to improve the accuracy of identifying Veterans with PNES based on ICD-10 diagnoses. We intend to get access to the DoD and link it to Veteran data.
Further research will be done into the epidemiology and prevalence of PNES among the Veteran population. An analysis will be preformed to see if there is a relationship between various risk factors and PNES as opposed to Epilepsy and how recognizing these risk factors can have an impact on clinical treatment.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Our manuscript describing suicide and seizures in a national cohort study of veterans is currently being reviewed by journal Neurology: Clinical Practice. This study describes the increased rates of suicide and suicide related behavior in patients PNES. A Poisson regression was used to calculate the relative risk of suicide across groups. Results revealed that Veterans with PNES (RR = 1.75, 95% CI 0.84-4.24) and veterans with epilepsy (RR = 2.19, 95% CI 2.10-2.28) had higher risk for suicide compared to general veteran population. Veterans with PNES or epilepsy had higher risk of suicide and SRB if they had comorbid alcohol abuse, illicit drug abuse, major depression, post-traumatic stress disorder (PTSD), and use of psychotropic medications.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

We identified the low accuracy of ICD-10 coding for PNES and discovered that this is due to coding error within the VA computer network in which seizure disorder is coded as F44.5 (conversion disorder with convulsions). We are currently taking steps to understand why this is occurring and how we can fix it. However, this has reduced our cohort size from a proposed 1,000 to 223. To combat this problem we have manually adjudicated each case based on electronic health record notes through VooGoo.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Yarden Bornovski, MD; Ebony Jackson-Shaheed, MPH; Stephanie Argraves, MS; Adrianna Hitchins, MD; Benjamin Tolchin, MD; Kei-Hoi Cheung, PhD; Joseph Goulet, PhD, MS; Melissa Skanderson, MS; Cynthia Brandt, MD; MaryJo Pugh, PhD; Hamada Altalib, DO, MPH; Suicide and Seizures, a National Cohort Study in Veterans; Journal Neurology: Clinical Practice; Under Review/Pending.

Yarden Bornovski, Stephanie Argraves, Ebony Jackson-Shaheed, Benjamin Tolchin, Joseph Goulet, Kei Cheung, Adrianna Hitchins, Hamada Altalib. Psychosis and Seizures in the Veteran Population (4651). Neurology Apr 2020, 94 (15 Supplement) 4651

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Galluzzo D, Bornovski Y, Goulet J, Argraves S, Jackson-Shaheed E, Cheung KH, Brandt C, Pugh MJ, Altalib H. Validating ICD-10 Code F44.5: A Preliminary Study on the Sensitivity and Specificity of Administrative Data for Conversion Disorder with Convulsions. Poster presented at AES December 2019. #4135

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

  Nothing to report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

  Nothing to report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

  Nothing to report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name:	Dr. Hamada Hamid Altalib
Project Role:	Primary Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Led the administration, team development and meetings, daily operations, data collection, and data analysis. Submitted two abstracts
Name:	Dr. Mary Jo Pugh
Project Role:	Co-Principal Investigator
Researcher Identifier (e.g. ORCID ID):	Orcid ID: 0000-0003-4196-7763
Nearest person month worked:	1
Contribution to Project:	Setting up Department of Defense data source and supervising

Name:	Dr. Kei-Hoi Cheung
Project Role:	Informatics Research Scientists
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Developed data extraction tool (Voogo) and is training data manager on setting up database

Name:	Dr. Joseph Goulet
Project Role:	Epidemiologist/Biostatistician
Researcher Identifier (e.g. ORCID ID):	0000-0002-0842-804X
Nearest person month worked:	1
Contribution to Project:	Senior statistician, study design, statistical analysis and interpretation, and edit manuscripts and reports.

Name:	Stephanie Argraves, MS
Project Role:	Data Manager
Researcher Identifier (e.g. ORCID ID):	0000-0002-6418-4449
Nearest person month worked:	5
Contribution to Project:	

Name:	Dr. Yarden Bornovski
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Data collection and research coordinator, institutional board review, data use agreements.

Name:	Ebony Jackson Shaheed, MPH
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	*0000-0001-8657-5814*
Nearest person month worked:	1
Contribution to Project:	Research Coordinator, IRB, Statistical analysis and interpretation, edit manuscripts and reports.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
<u>Organization Name:</u>
<u>Location of Organization: (if foreign location list country)</u>
<u>Partner's contribution to the project</u> (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Name:	Dr. Mary Jo Pugh
Project Role:	Co-Principal Investigator
Organization Name):	University of Utah- School of Medicine
Location of Organization:	Salt Lake City, Utah
Contribution to Project:	Setting up Department of Defense data source and supervising

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

Abstracts

- Poster was presented to American Epilepsy Society Annual Meeting 2019
- Abstract accepted by American Epileptic Society presented Dec 2019

Validating ICD-10 Code F44.5; A Preliminary Study on the Sensitivity and Specificity of Administrative Data for Conversion Disorder with Convulsions
Daniela Galluzzo, Yarden Bornovski, Stephanie Argraves, Kei H Cheung, Joseph Goulet, Ebony Jackson Shaheed, Cynthia Brandt, Mary Jo Pugh, Hamada Altalib.

Rationale: Despite a verified biomarker for diagnosis (video EEG), as well as guidelines for diagnosis from the International League Against Epilepsy (ILAE), validity still varies in ICD-10 coding for PNES. We performed a diagnostic accuracy study of the 10th International Classification of Diseases (ICD10) code to determine the sensitivity and specificity of F44.5 for psychogenic non-epileptic seizures (PNES).

Methods: The study population consisted of 876 Veterans, obtained from an ongoing study in the Veterans Administration of post 9/11 Veterans with PNES. The positive predictive value (PPV) was calculated for ICD-10 Code F44.5 using video EEG diagnosed PNES as the true positive group. Preliminary data is presented on 100 Veterans randomly selected from this cohort.

Results: Among 100 patients coded for ICD 10 F44.5, adjudication identified 55 Veterans with PNES: 11 (11%) Definite, 16 (16%) Probable, and 28 (28%) Possible, 3 (3%) with Epilepsy, and 42 (42%) without PNES or Epilepsy. The PPV of ICD-10 code F44.5 was 61% when coded for by any provider and increased to 73% when coded by a Neurologist.

Conclusions: Proper coding for PNES has immediate and long-term implications in patient care, including: communication amongst a multidisciplinary team, access to care and initiation of proper treatment, as well as future research studies. These preliminary results indicate discrepancy in coding for conversion disorders with convulsions. The PPV seems to depend on the level of department specialization. Further studies are warranted to confirm or refute these findings.

- Abstract was accepted to American Academy of Neurology April 2020.

Psychosis and Seizures in the Veteran Population (4651)

Yarden Bornovski, Stephanie Argraves, Ebony Jackson Shaheed, Joseph Goulet, Benjamin Tolchin, Mary Jo Pugh, Hamada Altalib.

Objective: Describe the relationship of epileptic and non-epileptic seizure with psychosis in the Veteran population

Intro/Background: The prevalence of psychotic disorders within the general population is estimated to be around 1-4%, but is higher (6%) among people with epilepsy[1-3]. Psychotic symptoms such as hallucinations, paranoia, and delusions may manifest as ictal or post-ictal phenomena[4]. Post-ictal irritability and aggression may be misdiagnosed as psychosis. Psychiatric comorbidities of psychogenic non-epileptic seizures (PNES) can result in accurate or inaccurate diagnoses of psychosis.

Methods: Electronic health records of post-9/11 Veterans were extracted (N= 801,883) to identify Veterans in VA care with a diagnosis of epilepsy (n = 10,994), PNES (n = 751) and general sample without seizures (n = 790,068)[5]. We examined the International Classification of Disease 9 and 10 (ICD) diagnoses of schizophrenia, psychosis NOS, and post-traumatic stress disorder (PTSD) within these groups.

Results: We found that 28% of epilepsy patients were coded for psychosis not otherwise specified (NOS) and 2% were coded with schizophrenia. Within the PNES sample, 31% were coded for psychosis NOS and 1% with schizophrenia, while in the sample without seizures, 5% were coded for psychosis NOS and 0.5% with schizophrenia. PTSD was 72% in the epilepsy sample, 83% within the PNES population, and 37% in the general sample. Of the general sample coded for psychosis, 9% had PTSD. Coding for psychosis were primarily mental health (55-58%), physiatry (13-15%), and neurology (1-2%).

Conclusions: The increased proportion of psychosis NOS within epileptic and PNES patients may represent a coding error within the EHR or may have important clinical implications. We will determine if the large proportion of psychosis NOS diagnoses is an EHR coding error or a result of peri-ictal phenomena, post-ictal agitation, or co-morbid psychosis. If results were due to coding error, this error disproportionately affects patients with epilepsy and PNES.

Manuscript Pending:

Suicide and Seizures, a National Cohort Study in Veterans

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Search Terms: All Neurology, Epilepsy, psychogenic non-epileptic seizures, non-epileptic seizures, suicide, suicide-related behavior.

Submission Type: Article
Title Character Count: 49
Number of Tables: 2
Number of Figures: 1

Word Count Abstract: 253
Word Count Paper: 1220

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Financial Disclosures:
Yarden Bornovski – salary is paid by a grant from the U.S. Department of Defense CDRMP (EP1600449).
Ebony Jackson-Shaheed – reports no disclosures
Stephanie Argraves – reports no disclosures
Adrianna Hitchins – reports no disclosures
Benjamin Tolchin - received research funding from a US Veteran Administration (VA)'s VISN1 Career Development Award, the VA Pain Research, Informatics, Multimorbidities, and Education (PRIME) Center of Innovation, and the C.G. Swebilius Trust. He has received honoraria from Columbia University Medical Center, the International League against Epilepsy, and the American Academy of Neurology.
Kei-Hoi Cheung – reports no disclosures
Joseph Goulet - reports no disclosures
Melissa Skanderson - reports no disclosures
Cynthia Brandt - reports no disclosures
MaryJo Pugh - reports no disclosures
Hamada Altalib – is on the scientific advisory board for Eisai, has received commercial research support from Eisai Medical Research, Engage Therapeutics, Pfizer, Sunovion, and UCB. Has received government research support from the Department of Defense Congressionally Directed Medical Research Programs Epilepsy Research Program (DOD CDMRP ERP) #EP160049, DOD CDMRP ERP #EP150013, Department of Veterans Affairs Health Service Research & Development Center of Innovation # CIN 13-407 COIN, and U.S. Department of Defense Office of Naval Research #N66001-08-C-2005

Study Funded by: Department of Defense Congressionally Directed Medical Research Programs Epilepsy Research Program (DOD CDMRP ERP) #EP160049

Abstract

Background: The increased rate of suicide associated with epilepsy has been described, but no studies have reported the rates of suicide and suicide related behavior (SRB) associated with psychogenic non-epileptic seizures (PNES).

Methods: This retrospective cohort study analyzed data from October 2002 to October 2017 within Veterans Health Administration (VHA) services. Of 801,734 veterans, 0.09% had PNES, 1.37% had epilepsy, and 98.5% had no documented seizures. Veterans coded for completed suicide, suicide attempts, and suicidal ideations were identified from electronic health records (EHR). The primary measure was the suicide-specific standardized mortality ratio (SMR) based on the number of suicide deaths and CDC national suicide mortality database. A Poisson regression was used to calculate the relative risk of suicide across groups.

Results: A total of 1,870 veterans (mean age [SD] 33.76 [7.81] years) completed suicide. Veterans with PNES (RR = 1.75, 95% CI 0.84-4.24) and veterans with epilepsy (RR = 2.19, 95% CI 2.10-2.28) had higher risk for suicide compared to general veteran population. Veterans with PNES or epilepsy had higher risk of suicide and SRB if they had comorbid alcohol abuse, illicit drug abuse, major depression, post-traumatic stress disorder (PTSD), and use of psychotropic medications. Conversely, those who were married or attained higher education were at decreased risk. . The SMR for completed suicide for PNES, epilepsy, and the comparison group was 2.65 (95% CI 1.95-5.52), 2.04 (95% CI 1.60 - 2.55), and 0.70 (95% CI 0.67 - 0.74), respectively.

Conclusions: Veterans with seizures (both psychogenic and epileptic) are at an increased risk for death by suicide and SRB than the comparison group. These findings suggest that while the pathophysiology of PNES and epilepsy are different, the negative impact of seizures is evident in the psychosocial outcomes in both groups.

Introduction:
Suicide is a common cause of increased mortality in people with seizures and the relationship between seizures and suicide is complex and controversial.1, 2 Anti-seizure medications (ASMs) have a black box warning for increased risk for suicide.3 However, several large cohort studies demonstrate that epilepsy increases risk of completed suicide and suicide related behavior (SRB) independent of ASMs, even after successful epilepsy surgery.4-6 Changes in neural networks may make people with epilepsy more vulnerable to mood disorders.7, 8 However, the relationship of psychosocial stressors related to seizures and suicide risk is understudied. For instance, social stigma and isolation, driving restrictions, and decreased employability may play a major role in suicide risk. People with psychogenic non-epileptic seizures (PNES) face similar psychosocial challenges to people with epilepsy and most carry the diagnosis of epilepsy for years prior to the PNES diagnosis. However, they do not suffer from the same neuropathology as people with epilepsy.9 Therefore, comparing the suicide rate of people with epilepsy to people with PNES may provide insight into the role of psychosocial forces in suicide and SRB.

Methods:
Suicide related behavior (SRB) was defined as the presence of suicidal ideation and/or suicide attempts as per ICD-10 coding (see Appendix Table 1 for ICD-10 codes used). Groups were

divided into veterans coded for PNES, veterans coded for epilepsy, and the "general veteran group" composed of veterans without coding for PNES or epilepsy2, 10. People with combined PNES and epilepsy were removed from the analysis. The sample (n = 801,734) was drawn from the Women Veterans Cohort Study, which includes men and women veterans enrolled in VHA care from October 2002 to 2017.10 A validated set of ICD-10 codes for intentional or undetermined violent deaths (defined as completed suicide) was obtained from the VA Suicide Data Repository.11, 12

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol was approved by VA Connecticut Healthcare System Institutional Review Board as well as The U.S. Army Medical Research and Development Command Office of Research Protection Office.

The datasets generated and/or analyzed during the current study are not publicly available due VA privacy and information security policies. De-identified data may be requested and shared with the appropriate permissions and approvals.

Statistical Analysis

Standardized Mortality Ratio (SMR) was calculated to compare the suicide mortality rates among veterans with PNES, veterans with epilepsy, and the general veteran group in comparison to expected suicide deaths over a 16-year period. Data was stratified by gender (female/male) and age (15-24, 25-34, 35-44, 45-54, 55-64, 64-74, 75-84 years-old). Data for the standardized mortality ratio was obtained from the CDC (Matthew M. Zack, CDC medical epidemiologist, email communication, February 11, 2020).

Chi-square tests were used to examine bivariate relationships between categorical variables and t-tests or nonparametric tests, as appropriate, were used for continuous variables. Because our study is a cohort study and the primary outcomes were rare events over time, we used Poisson regression with a log link and robust variance estimates to calculate relative rates of suicide and suicide related behavior (RR) and 95% confidence intervals (CI). The index date used for suicide related behavior for veterans with PNES and Epilepsy was the first incident recorded, as for suicide it is a one-time event. Demographic factors include gender and race. The Covariates are alcohol abuse, drug abuse, major depression, PTSD, psychotropic, educated, and married. TBI and Anxiety as covariates were removed from the final Poisson model as there was no statistical significance. To control for potential confounding that could distort the risk estimates, demographic clinical variables that were significant in bivariate analyses were entered into the model as covariates. An alpha level of 0.05 was considered statistically significant. All statistics were conducted using SAS version 9.4 (Cary North Carolina).

Results:

The cohort included a total of 801,734 veterans: 752 veterans with PNES, 10,994 veterans with epilepsy and 789,988 veterans without PNES or epilepsy (defined as Other) (Table 1). The mean age was 31.85 years old (SD 9.07) at first visit and 33.76 years old (SD 7.81) for suicide. There were 1,870 total deaths from suicide: 0.80% veterans with PNES, 0.65% of veterans with epilepsy, and 0.23% of veterans in the general veteran group.

SRB was present in 29% of veterans with PNES, 24% of veterans with epilepsy, and 5.6% of the general veteran group. The SMR was calculated using CDC national suicide mortality data to standardize for age and gender. The SMR for PNES, epilepsy, and the general veteran group was

2.65 (95% CI = 1.95-5.52), 2.04 (95% CI = 1.60 - 2.55), and 0.7 (95% CI = 0.673 - 0.738), respectively (Figure 1).

The relative rates for suicide and SRB from Poisson regression are shown in Table 2. Veterans diagnosed with PNES have a RR of 1.75 (95% CI = 1.51-2.02; p<.0001) times that of epileptic veterans for committing suicide, and a RR of 3.82 (95% CI =3.32-4.39; p<.0001) times likely to commit suicide compared to the general population. Epileptic veterans have a RR of 2.19 (95% CI =2.10-2.28; p<.0001) times the risk of suicide as opposed to the other group or general population. For those veterans with suicide related behavior, it is reported that veterans with PNES have a RR of 1.61 (95% CI=1.51-1.73; p<.0001) compared to epileptic veterans, and a RR of 3.65 (95%CI=3.42-3.90; p<.0001) compared to the general population (other group). Epileptic veterans are 2.26 (95% CI=2.22-2.31; p<.0001) times as likely to engage in suicide related behavior than the general population. Female veterans with PNES are 0.48 (95%CI=0.46-0.50; p<.0001) times as high a risk of committing suicide compared to their male counterparts, and 0.96 (95% CI=0.95-0.98; p<.0001) times as high a risk for engaging in suicide related behavior. Of the racial group, veterans who classified as Other compared to White veterans were at a higher RR 0.81 (95%CI=0.79-0.83; p<.0001) of committing suicide compared to Black 0.45 (95%CI=0.44-0.46; p<.0001) and Hispanic 0.56 (95%CI=0.55-0.58; p<.0001) veterans. For those veterans with PNES engaging in suicide related behavior the Black population has the greatest risk with a RR of 0.93 (95%CI=0.92-0.94; p<.0001). Anxiety and TBI were significantly associated with SRB only (p<0.0001). Of comorbid covariates veterans with PNES have the greatest risk of suicide if they are engaging in drug abuse with a RR of 1.92 (95%CI=1.88-1.96; p<.0001). Veterans with PNES and are on Psychotropic medication have the highest risk of engaging in suicide related behavior with a RR of 8.38 (95% CI=8.15-8.61; p<.0001).

Discussion:

Veterans with epileptic and psychogenic non-epileptic seizures are both approximately two times more likely to commit suicide and exhibit SRB than veterans in the general veteran group (Figure 1). Increased risk of SRB has been attributed to anti-seizure medications, psychiatric comorbidities, psychosocial stressors, and changes in neurocircuitry. The underlying neurobiology of epilepsy and PNES fundamentally differ. Therefore, the high risk of suicide and SRB in both populations are likely not due to a common neurobiological substrate but may be due to the shared psychosocial stressors of unpredictable seizures and high levels of stigma.

Mood disorders and substance abuse are strongly associated with suicidality. The diagnosis of a mood disorder is associated with a 35-60% increased risk of suicide and over 60% of those who commit suicide were previously diagnosed with a mood disorder.13 Our study demonstrated similar increased risk with depression, psychotropic medication use, alcohol abuse, and drug abuse. As reviewed elsewhere, education and marriage are associated with reduced risk of suicide14, 15. TBI and anxiety were not significantly associated with completed suicide, but the association became significant for SRB. However, it is important to note that these risk factors are not mutually exclusive, as TBI could cause depression and anxiety, and PTSD could drive alcohol and drug abuse.

PTSD is an important risk factor for suicidality and mental health comorbidities. While PTSD is a confounder to suicide and SRB, it doesn't fully explain the increased suicide seen in PNES and epilepsy. When analyses were controlled for PTSD, the association between suicide and seizures

was still significant. Thus, higher rates of PTSD only partially explain the increased rates of suicide among veterans with epilepsy and PNES.
The decreased SMR in the general veteran group (SMR = 0.7) is consistent with current literature. Hoffmire et. al (2015) reported that veterans who died from suicide were older than non-veterans who died from suicide.16 Veterans who utilize VHA services may have a decreased suicide risk compared to those who don't.17
Further research should explore the association of psychosocial risks and protective factors in people with seizures and suicidality. PNES is a functional neurological disorder that is diagnosed by neurologists and treated by mental health professionals, yet many patients still suffer poor outcomes as demonstrated by the increased suicide risk.

Limitations:
External validity to the general US population may be limited given that our study was restricted to patients receiving primary care through the VA, who are more likely to be men and have more comorbidities than counterparts receiving care outside the VA. The majority of our population was between 30-49 years old and male due to the inclusion criteria of the database we used.
We used healthcare claims databases (ICD-9 and ICD-10) that are created for administrative and reimbursement purposes and not for research purposes, which have varying degrees of accuracy.
Due to the limited sample size for suicide in PNES, the confidence intervals are wide for suicide and SRB.

Conclusion:
Veterans with PNES and veterans with epilepsy are both at significantly increased risk for suicide and SRB when compared to the general population. The high risk of suicide among veterans with different types of seizures may be due to shared psychosocial stressors. Future research will look at whether PTSD therapy and PNES-driven psychotherapy is protective for suicide and whether delayed diagnosis of PNES plays a part in the increased suicidality.

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Abbreviations:
DoD: Department of Defense
EHR: Electronic Health Records
FND: Functional Neurological Disorder
GEE: Generalized Estimating Equations
OEF: Operation Enduring Freedom
OIF: Operation Iraqi Freedom
OND: Operation New Dawn
PE: Prolonged Exposure
PNES: Psychogenic Non-epileptic Seizures
PTPNES: post-traumatic PNES
PTSD: Post-Traumatic Stress Disorder
SSRI: Selective serotonin reuptake inhibitor
TBI: Traumatic Brain Injury
SRB: Suicide related behavior
ASM: Anti-seizure medication
VA: Veterans Affairs
HER: Electronic health record
VHA: Veterans Health Administration
VEEG: Video-Electroencephalogram
CI: Confidence Interval
ICD: International Statistical Classification of Diseases and Related Health Problems

Declarations:

Ethics approval and consent to participate

Ethical approval was granted by the VA Connecticut Healthcare System Institutional Review Board and by the U.S. Army Medical Research Human Research Protection Office.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due VA privacy and information security policies.

Competing interests

The authors declare that they have no competing interests

Funding

The study is funded through the U.S. Department of Defense Congressionally Directed Medical Research Programs (EP1600449).

Authors' contributions

HA, BF, MJP designed the project. HA secured funding for the project and was responsible for ethics approval. All authors contributed to the conception and design of the study, interpretation of data, draft composition and review, accountability for the work, and final approval of the final manuscript.

Acknowledgements

We would like to thank members of the VA Connecticut Healthcare System Pain, Research, Informatics, Medical comorbidities and Education Center of Innovation and the Yale Center for Neuro-epidemiology and Clinical Neurological Research for their input and feedback

Table 1. Demographics for All Deaths in veterans (n = 801,734, mean age = 31.8) with PNES, Epilepsy and Veterans in the general veteran group (identified as Other). PNES = psychogenic non-epileptic seizures, PTSD = post-traumatic stress disorder, TBI = traumatic brain injury, SRB = suicide related behavior.

Table 1	**PNES (N=752)**	**Epilepsy (N=10994)**	**Other (N=789988)**
Demographics, No. (%)	**16**	**531**	**8301**
Male	15 (93.8%)	494 (93.0%)	7758 (93.5%)
Age			
<30	11 (68.8%)	317 (59.7%)	4095 (49.3%)
30-49	4 (25%)	191 (36%)	3305 (39.8%)
50+	1 (6.2%)	23 (4.3%)	901 (10.9%)
Comorbidities			
Alcohol Abuse	6 (37.5%)	266 (50.09%)	2801 (33.74%)
Drug Abuse	9 (56.25%)	220 (41.43%)	1907 (22.97%)
Anxiety	9 (56.25%)	237 (44.63)	2387 (28.75%)
Depression	8 (50.00%)	190 (35.78%)	1812 (21.82%)
PTSD	13 (81.25%)	372 (70.05%)	4211 (50.72%)
TBI	7 (43.75%)	145 (27.3%)	702 (8.45%)
SRB	8 (50%)	142 (26.74%)	1164 (14.02%)
Suicide (Intentional and Undetermined Death)	6 (37.5%)	71 (13.37%)	1793 (21.60%)

Table 2. Poisson regression of veterans with seizures (PNES and epilepsy) and associated risk factors compared to the general veteran group. PNES = psychogenic non-epileptic seizures, PTSD = post-traumatic stress disorder, TBI = traumatic brain injury, SRB = suicide related behavior.

Characteristics	**Suicide RR (95%CI)**	**P**	**Suicide Behavior RR (95%CI)**	**P**
PNES vs. Epilepsy	1.75 (1.51-2.02)	**.0001**	1.61 (1.51-1.73)	**.0001**
PNES vs. Other	3.82 (3.32-4.39)	**.0001**	3.65 (3.42-3.90)	**.0001**
Epilepsy vs. Other	2.19 (2.10-2.28)	**.0001**	2.26 (2.22-2.31)	**.0001**
Female vs. Male	0.48 (0.46-0.50)	**.0001**	0.96 (0.95-0.98)	**.0001**
Black	0.45 (0.44-0.46)	**.0001**	0.93 (0.92-0.94)	**.0001**
Hispanic	0.56 (0.55-0.58)	**.0001**	0.89 (0.87-0.90)	**.0001**
Other	0.81 (0.79-0.83)	**.0001**	0.81 (0.80-0.82)	**.0001**
White	-	**-**	-	**-**
Alcohol Abuse	1.72 (1.69-1.76)	**.0001**	1.96 (1.94-1.98)	**.0001**
Drug Abuse	1.92 (1.88-1.96)	**.0001**	2.65 (2.63-2.68)	**.0001**
Major Depression	1.51 (1.48-1.54)	**.0001**	2.43 (2.40-2.45)	**.0001**
PTSD	1.19 (1.17-1.21)	**.0001**	1.53 (1.52-1.55)	**.0001**
Psychotropic	1.49 (1.46-1.53)	**.0001**	8.38 (8.15-8.61)	**.0001**
Educated	0.69 (0.67-0.70)	**.0001**	0.74 (0.72-0.75)	**.0001**
Married	0.81 (0.80-0.83)	**.0001**	0.93 (0.92-0.94)	**.0001**