Study of Pseudobulbar Affect Symptoms in Veterans with Possible Traumatic Brain Injury

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Poll Question

What is your role in the VHA? (select all that apply):

a) Psychologist/Psychiatrist
b) Other Specialty
c) VA researcher
d) Non-VA researcher
e) Management/policy maker
Poll Question

Are you familiar with traumatic brain injury (TBI) (please select one)?

a) Yes
b) No
c) Unsure
Challenges of TBI Rehabilitation in OEF/OIF Veterans

Outline

• The scope of the challenge: who is of particular concern for the VA in the coming years?
• Why does this cohort represent such a challenge?
• Considerations for treatment.
The Scope: mTBI

In the US military, TBI is the most common type of physical injury sustained by OEF/OIF service members, and EXPLOSION OR BLAST INJURY by explosive devices (improvised explosive devices, landmines, rockets, etc.) is the most common cause.

APPROXIMATELY 75% OF ALL TBI’S ARE CLASSIFIED AS MILD*

*Center for Disease Control & Prevention, 2010
mTBI

<table>
<thead>
<tr>
<th>Criteria: must be &gt;0 for one of the following:</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of Consciousness (LOC)</td>
<td>None</td>
<td>&lt;5 minutes</td>
<td>&gt; 5 minutes</td>
</tr>
<tr>
<td>Post Traumatic Amnesia (PTA)</td>
<td>0-15 minutes</td>
<td>&lt;24 hours but &gt; 15 minutes</td>
<td>&gt;24 hours</td>
</tr>
<tr>
<td>Alteration of Mental Status (AMS)</td>
<td>0-15 minutes</td>
<td>&lt;24 hours but &gt; 15 minutes</td>
<td>&gt;24 hours</td>
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</table>

Developed based on Bailes & Cantu, 2001
Why does this cohort represent such a challenge?

HETEROGENIETY!
Simultaneity of Physical and Psychological Trauma in OEF/OIF
mTBI is a Poly-Morbid Condition

TRACTS COHORT: OEF/OIF VETERANS WITH mTBI (n=81)

- PTSD 80%
- SLEEP Disturbance 80%
- Other ANXIETY Disorder 17%
- MOOD Disorder 42%
- ALCOHOL Abuse/Dependence 24%
- OTHER SUBSTANCE Abuse/Dependence 2%
- PAIN 73%
- Sleep Disturbance 80%
SO WHAT?

MANY OF THE CO-MORBID CONDITIONS SHARE THE SAME UNDERLYING NEURAL STRUCTURES AND SYSTEMS.

For example:
### Not surprising….Shared Cognitive Dysfunction

<table>
<thead>
<tr>
<th>Persistent mTBI</th>
<th>PTSD</th>
<th>Alcohol Abuse/Dependence</th>
<th>Cardiovascular Risk</th>
<th>Pain</th>
<th>Sleep</th>
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<tbody>
<tr>
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<td>Re-experiencing</td>
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Poll Question

Are you familiar with Pseudobulbar Affect (PBA) (please select one)?

a) Yes
b) No
c) Unsure
Pseudobulbar affect (PBA)

- PBA is a neurological syndrome characterized by involuntary, uncontrollable, exaggerated, and often inappropriate outbursts of crying and/or laughing

Schiffer & Pope, 2005
PBA Etiology

• PBA develops in the context of numerous neurological conditions including:
  – Stroke
  – Multiple sclerosis (MS)
  – Amyotrophic lateral sclerosis (ALS)
  – Parkinson’s disease
  – Alzheimer’s disease
  – Traumatic brain injury

Brooks et al., 2013; Work et al., 2011; Wortzel et al., 2008
PBA: Another Piece to the Puzzle?

- PBA is prevalent among people with history of brain injury, but rates of recognition and diagnosis are low for several reasons:
  - PBA-related crying episodes may be mistaken as a symptom of depression or post-traumatic stress disorder (PTSD)
  - PBA may coexist with depression or PTSD
  - Patients with TBI may have cognitive impairment that interferes with their insight or reporting of symptoms
Importance of PBA Symptoms Recognition

• Increased recognition of PBA symptoms can:
  – Facilitate diagnosis
  – Help differentiate from other comorbid neuropsychiatric symptoms affecting patients with TBI
  – Enable appropriate management
Study: PBA Symptom Screening in OEF/OIF/OND Veterans

• Objectives
  – Estimate the occurrence of PBA symptoms in OEF/OIF/OND Veterans who screened positive for TBI
  – Evaluate the concordance between the two survey instruments used to assess the occurrence of PBA symptoms:
    • A single PBA screen question*
    • The Center for Neurologic Study-Lability Scale (CNS-LS) questionnaire†

* Colamonico et al., 2012
† Moore et al., 1997
Study Population

• Inclusion Criteria:
  – OEF/OIF/OND Veterans receiving healthcare in the VA New England Healthcare System (VISN-1)
  – Screened positive for TBI on the VA standard TBI screen

• Exclusion Criteria:
  – Current ICD-9 diagnosis code for:
    • Bipolar disorder
    • Schizophrenia
    • Other psychotic disorder (except psychosis not otherwise specified due to trauma-related hallucinations)
VA Primary TBI Screen

1. During any of your deployment(s) did you ever experience any of the following events?
   a) Blast or explosion
   b) Vehicular accident/crash (including aircraft)
   c) Fragment wound or bullet wound above the shoulders
   d) Fall

2. Did you have any of these symptoms immediately afterward?
   a) Losing consciousness/“knocked out”,
   b) Being dazed, confused, or “seeing stars”
   c) Not remembering the event
   d) Concussion
   e) Head injury

3. Did any of the following problems begin or get worse afterwards?
   a) Memory problems or lapses
   b) Balance problems or dizziness
   c) Sensitivity to bright light
   d) Irritability
   e) Headaches
   f) Sleep problems

4. In the past week, have you had any of the symptoms from Section 3?
Data Sources

• Mailed survey instruments
  – A single PBA screen question
  – CNS-LS questionnaire

• VA databases
  – Demographics
  – Clinical
  – VA Primary and Secondary TBI screens
Assessment of PBA Symptoms: Screening Question

Please circle the response that best describes your experience.

Have you ever experienced involuntary episodes of crying and/or laughing that were exaggerated or even contrary to how you felt at the time?
– Yes – No – Not sure
Assessment of PBA Symptoms: CNS-LS

Regardless of answering yes, no, or not sure to the question above, please read each statement below and fill in the circle that best describes the degree to which each item applies to you. (Scored 1 to 5 on each question, total 7- to 35-point scale)

During the past week:

- 1. There are times when I feel fine one minute, and then I’ll become tearful the next over something small or for no reason at all.
- 2. Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren’t funny.
- 3. I find myself crying very easily.
- 4. I find that even when I try to control my laughter, I am often unable to do so.
- 5. There are times when I won’t be thinking of anything happy or funny at all, but then I’ll suddenly be overcome by funny or happy thoughts.
- 6. I find that even when I try to control my crying, I am often unable to do so.
- 7. I find that I am easily overcome by laughter
Assessment of PBA Symptoms

• Screen positive for PBA Symptoms if meet at least one of the following criteria:
  – CNS-LS ≥ 13
  – “Yes” response on single screening question

• Screen positive for moderate/severe PBA symptoms if CNS-LS ≥ 21
Study Sequence

Study Population

Mailed Questionnaires
N = 3,954 (92%)

Initial TBI Screen Positive
N = 4,283

VA Clinical Data System
N = 4,283

Outcomes

Data Sources and Collection

Comprehensive TBI evaluation
N = 2,467 (58%)

Modified CNS-LS Questionnaire
N = 758 (19%)

Demographic Data
N = 4,283

Diagnosis, Pharmacy
N = 4,283

EQ-5D HR QOL Questionnaire
N = 758 (19%)

PBA Symptoms by CNS-LS

PBA Symptoms by Involuntary Episodes

Characterization of Veterans with TBI and PBA symptom

Confirmed TBI
N = 1,316 (53%)

Yes – 69.6%
No – 30.4%

Yes – 60.4%
No – 24.3%

89% mild TBI
11% moderate/severe TBI
Results

• Characteristics of our study population (n=4,283):
  – Predominantly male (95%)
  – Average age of 34.5 years (SD = 8.8)
  – High prevalence of behavioral and mental health conditions, including:
    • Pain (50%)
    • PTSD (46%)
    • Depression (26%)
    • Anxiety disorders (17%)
Survey Response

- 758 (19.2%) respondents out of the 3,954 in the study sample with accurate mailing addresses
- Compared to non-respondents, respondents were more likely to be:
  - Older
  - White
  - Married
  - College graduates
Survey Response

• Additionally, respondents were more likely than non-respondents to have:
  – Current depression diagnosis (31.0% vs. 25.6%)
  – Prescription for:
    • Antidepressants (41.7% vs. 35.7%)
    • Anti-epileptics (17.4% vs. 13.4%)
# Comorbidities and Medications by PBA Symptom Status

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>CNS-LS Threshold (n=737)*</th>
<th>Involuntary Episodes (n=605)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBA Positive (n=513)</td>
<td>PBA Negative (n=224)</td>
</tr>
<tr>
<td>Hyperlipidemia³</td>
<td>107 (20.9%)</td>
<td>43 (19.2%)</td>
</tr>
<tr>
<td>Hypertension⁴</td>
<td>77 (15.0%)</td>
<td>29 (13.0%)</td>
</tr>
<tr>
<td>Pain Conditions</td>
<td>284 (55.4%)</td>
<td>112 (50.0%)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>48 (9.4%)</td>
<td>17 (7.6%)</td>
</tr>
<tr>
<td>Back/neck pain</td>
<td>173 (33.7%)</td>
<td>71 (31.7%)</td>
</tr>
<tr>
<td>Other arthropathy</td>
<td>176 (34.3%)</td>
<td>71 (31.7%)</td>
</tr>
<tr>
<td>Headache/migraine</td>
<td>102 (19.9%)</td>
<td>31 (13.8%)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Mental Health Problems</th>
<th>CNS-LS Threshold (n=737)*</th>
<th>Involuntary Episodes (n=605)*</th>
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<tbody>
<tr>
<td></td>
<td>PBA Positive (n=513)</td>
<td>PBA Negative (n=224)</td>
</tr>
<tr>
<td>Major Depression</td>
<td>177 (34.5%)</td>
<td>49 (21.9%)</td>
</tr>
<tr>
<td>PTSD</td>
<td>275 (53.6%)</td>
<td>72 (32.1%)</td>
</tr>
<tr>
<td>Anxiety Disorders</td>
<td>103 (20.1%)</td>
<td>29 (13.0%)</td>
</tr>
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</table>

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<thead>
<tr>
<th>Substance Abuse</th>
<th>CNS-LS Threshold (n=737)*</th>
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<tbody>
<tr>
<td></td>
<td>PBA Positive (n=513)</td>
<td>PBA Negative (n=224)</td>
</tr>
<tr>
<td>Alcohol-Related</td>
<td>85 (16.6%)</td>
<td>25 (11.2%)</td>
</tr>
<tr>
<td>Drug-Related</td>
<td>52 (10.1%)</td>
<td>17 (7.6%)</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>88 (17.2%)</td>
<td>28 (12.5%)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Prescription Medication</th>
<th>CNS-LS Threshold (n=737)*</th>
<th>Involuntary Episodes (n=605)*</th>
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<tbody>
<tr>
<td></td>
<td>PBA Positive (n=513)</td>
<td>PBA Negative (n=224)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>236 (46.0%)</td>
<td>70 (31.3%)</td>
</tr>
<tr>
<td>Opioids</td>
<td>97 (18.9%)</td>
<td>17 (7.6%)</td>
</tr>
<tr>
<td>Sedative/Hypnotics</td>
<td>90 (17.5%)</td>
<td>22 (9.8%)</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>102 (19.9%)</td>
<td>25 (11.2%)</td>
</tr>
</tbody>
</table>

*Data reported for subjects with complete CNS-LS responses. Involuntary Episodes “Unsure” responses omitted.

Underlined values are significantly different (p < 0.05) between PBA symptom positive and negative within survey instrument.
PBA Symptoms

• The majority of Veterans screened positive for PBA symptoms
  – 70% had a CNS-LS ≥ 13
  – 60% responded “yes” on the single screening question
  – 62% screened positive on both measures

• 22% screening positive for moderate/severe PBA symptoms (CNS-LS ≥ 21)
Concordance between CNS-LS threshold and involuntary episode screening question

<table>
<thead>
<tr>
<th>CNS-LS Threshold ≥ 12</th>
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</thead>
<tbody>
<tr>
<td>CNS-LS Positive</td>
<td>CNS-LS Negative</td>
</tr>
<tr>
<td>Involuntary Episodes - Yes</td>
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<tr>
<td>390 (66.0%)</td>
<td>56 (9.5%)</td>
</tr>
<tr>
<td>Involuntary Episodes- No</td>
<td></td>
</tr>
<tr>
<td>30 (5.1%)</td>
<td>115 (19.5%)</td>
</tr>
<tr>
<td>420 (71.1%)</td>
<td>171 (28.9%)</td>
</tr>
</tbody>
</table>

Sensitivity = 0.87, Specificity = 0.79, PPV = 0.93
Summary

- Occurrence of PBA is common among OEF/OIF/OND Veterans who screened positive for TBI
  - 60 – 70% of respondent Veterans report PBA symptoms
- Veterans who reported PBA symptoms (CNS-LS ≥ 13) have significantly higher rates of:
  - Depression and PTSD
  - Use of anti-depressants, opioids, sedatives, and anti-epileptics.
Summary

• High concordance between the single screening question and the CNS-LS seven-item questionnaire (Se=0.87, Sp=0.79, PPV = 0.93)
• The sensitivity and specificity were not significantly different when using a threshold of CNS-LS≥13 (Se=0.82, Sp=0.83), rather than the optimal threshold of CNS-LS≥12
  – Very similar to those reported for ALS patients
Limitations

• Study sample limited to OEF/OIF/OND Veterans who received care at a VA in the New England region
  – This sample closely resembles the demographic characteristics of a national cohort of younger US Veterans
  – Thus, results could be generalized to a national sample of OEF/OIF/OND Veterans who screened positive for TBI

Eber et al., 2013
Limitations

- Included all Veterans who screened positive on the VA primary TBI screen to maximize number of respondents for the PBA questionnaires
  - False positive screens for TBI may occur if the Veteran has other conditions, including
    - PTSD
    - Other conditions that have concussion-like symptoms (e.g. hearing loss and vestibular changes)
  - Parallel analyses in the subset of Veterans with confirmed TBI on the VA secondary TBI evaluation yielded very similar results
Limitations

• This study employed a cross-sectional study design
  – Unable to determine the causal directional of the association between TBI and PBA symptoms
  – However, minimized potential retrospective reporting biases by obtaining clinical and TBI information from electronic medical records and standardized TBI reports.
Limitations

• Population prevalence cannot be estimated because of potential biases in survey response
  – Respondents and non-respondents were very similar on clinical characteristics unrelated to PBA (e.g., hypertension and hyperlipidemia), suggesting that the potential biases are minimal.
Conclusions

• This study provides another piece of a very complicated puzzle of trying to understand the mental and physical needs of our returning service members and Veterans.
  – Our findings highlight the previously unrecognized presence of PBA symptoms, in addition to other comorbidities, including PTSD and depression.
Conclusions

- PBA and other mental health disorders share highly interactive underlying neurological circuitry
- Treatment must be multifaceted and not targeted to a single condition
  - Example: Antidepressants may be ineffective in controlling PBA symptoms
    - A substantial proportion of Veterans report PBA symptoms despite use of antidepressant medications
Use a Patient-Centered Approach!!
ONE SIZE WILL NOT FIT ALL
Clinical Implications

• This study suggests that clinicians should regularly screen for PBA symptoms in Veterans who may have sustained a TBI while in service

• A simple screening question asking about involuntary episodes of laughing and crying:
  – Equally as effective as assessing the presence of PBA symptoms using the CNS-LS questionnaire
  – May help with feasibility of screening in everyday clinical practice
  – May provide signals for required differential diagnosis
Acknowledgements

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Questions??