Neuropsychiatric Aspects of Traumatic Brain Injury

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Military seeks test for brain injury

Joyce Howard Price
THE WASHINGTON TIMES

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The Pentagon is funding research to develop a blood test to gauge the severity of head wounds while the victim is still on the battlefield.

"The head is less than 9 percent of the body, yet it gives us 25 percent of the [combat] hits," said Lt. Col. Geoffrey Ling, a physician and director of neuro-intensive care at the Walter Reed Army Medical Center. "What's more, over 50 percent of the soldiers who die [from combat wounds] after reaching medical care have head injuries."

Yet the military has no diagnostic tool to help a combat medic in the field determine if a soldier suffering from a head wound has any chance of survival and should be transported to a hospital.

"If we have a few drops of blood and can use that to determine whether someone [with a head wound] is mildly, severely or moderately injured, that would be a huge contribution to decision-making" by a medic on the battlefield, Col. Ling said Friday in an interview.
Since the former National Football League player Andre Waters killed himself in November, an explanation for his suicide has remained a mystery. But after examining remains of Mr. Waters's brain, a neuropathologist in Pittsburgh is claiming that Mr. Waters had sustained brain damage from playing football and he says that led to his depression and ultimate death.
At least 1.4 million TBIs occur in the United States each year.*

- 50,000 Deaths
- 235,000 Hospitalizations
- 1,111,000 Emergency Department Visits
- ??? Receiving Other Medical Care or No Care

CDC, 2006

* Average annual numbers, 1995-2001

57 million living With TBI Worldwide

* At least 1.4 million TBIs occur in the United States each year.*
Traumatic Brain Injury (TBI)

- Neurobiological Injury
- Traumatic Event
- Chronic Medical Illness
TBI as Neurobiological Injury

• Primary effects of TBI
  – Contusions, diffuse axonal injury

• Secondary effects of TBI
  – Hematomas, edema, hydrocephalus, increased intracranial pressure, infection, hypoxia, neurotoxicity, inflammatory response, protease activation, calcium influx, excitotoxin & free radical release, lipid peroxidation, phospholipase activation

• Can affect serotonin, norepinephrine, dopamine, acetylcholine, and GABA systems
Examples of Neuropsychiatric Syndromes Associated with Neuroanatomical Lesions

- Lateral orbital pre-frontal cortex
  - Irritability - Impulsivity
  - Mood lability - Mania
- Anterior cingulate pre-frontal cortex
  - Apathy - Akinetic mutism
- Dorsolateral pre-frontal cortex
  - Poor memory search - Poor set-shifting / maintenance
- Temporal Lobe
  - Memory impairment - Mood lability
  - Psychosis - Aggression
- Hypothalamus
  - Sexual behavior - Aggression
Neuropathology in TBI and Depression

- Left dorsolateral frontal lesions or left basal ganglia lesions are associated with MDD in acute TBI and stroke (Federoff et al., 1992, Robinson et al., 1985)
- Disruption of frontal lobe - basal ganglia circuits is associated with MDD in TBI (Mayberg, 1994)
- Decreased glucose metabolism in orbital-inferior frontal and anterior temporal cortex is associated with MDD in TBI, CVA, Parkinson’s (Mayberg, 1994)
- Serotonergic fibers have been implicated in the pathogenesis of arousal, sleep and depression in both the general population and brain-injured patients
- Frontal lobe damage from TBI is associated with reduced brain serotonergic function (VanWoerkom et al., 1977)
- MDD is associated with reduced left prefrontal gray matter volumes, esp. ventrolateral & dorsolateral regions (Jorge et al., 2004)
TBI as Traumatic Event

• **PTSD Prevalence:** 11-27% *
  – Possibly more prevalent in mild TBI
  – Mediated by implicit memory or conditioned fear response in amnestic patients?

• **PTSD Phenomenology:** **
  – Intrusive memories: 0-19%
  – Emotional reactivity: 96%
  – Intrusive memories, nightmares, emotional reactivity had highest predictive power

• Anxiety often comorbid with / prolongs depression

** Warden et al 1997, Bryant et al 2000
TBI as Chronic Illness (the “Silent Epidemic”)

- 80,000-90,000 new TBI survivors experience onset of long-term disability annually
- About 1 in 4 adults with TBI is unable to return to work 1 year after injury
- 5.3 million Americans (2% of U.S. population) currently live with TBI-related disabilities
  - Based on hospitalized survivors only
- 65% of costs are accrued among TBI survivors
- Annual acute care and rehab costs of TBI = $9 - $10 billion *
- Estimated annual lifetime costs of TBI survivors in year 2000 = $60 billion **

* NIH Consensus Development Panel on Rehabilitation, 1999
Figure 1–20. Lifetime costs of head injury, 1985 (by severity of injury). *Source.* Max et al. 1991.
TBI-associated Disability

• “Postconcussive Symptoms”
• Cognitive
• Physical: sensory and motor
• Emotional
• Vocational
• Social
• Family
Neuropsychiatric Sequelae

- Delirium
- Depression / Apathy
- Mania
- Anxiety
- Psychosis
- Cognitive Impairment
- Aggression, Agitation, Impulsivity
- Postconcussive Symptoms
<table>
<thead>
<tr>
<th>Psychiatric</th>
<th>Neurologic/Medical</th>
<th>Social</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premorbid</td>
<td>Neurologic illness</td>
<td>Social, family, vocation</td>
</tr>
<tr>
<td>Psych disorders &amp; sx.</td>
<td>Lesion location, size,</td>
<td>Rehabilitation situation</td>
</tr>
<tr>
<td>Personality traits</td>
<td>pathophysiology</td>
<td>and stressors</td>
</tr>
<tr>
<td>Coping styles</td>
<td>Other medical illness</td>
<td>Functional impairment</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>Other indirect sequelae (e.g., pain,</td>
<td>Medicolegal</td>
</tr>
<tr>
<td>Medication side effects</td>
<td>sleep disturb)</td>
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<tr>
<td>&amp; interactions</td>
<td>Medication side effects</td>
<td></td>
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<tr>
<td>Psychodynamic sig. of neurologic illness</td>
<td>&amp; interactions</td>
<td></td>
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<tr>
<td>Family psych. history</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Roy-Byrne P, Fann JR. APA Textbook of Neuropsychiatry, 1997
# Neuropsychiatric Evaluation and Treatment: Workup

<table>
<thead>
<tr>
<th><strong>Psychiatric</strong></th>
<th><strong>Neurologic/Medical</strong></th>
<th><strong>Social</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric history &amp; examination</td>
<td>Medical history and physical examination</td>
<td>Interview family, friends, caregivers</td>
</tr>
<tr>
<td>Neuropsychological testing</td>
<td>Appropriate lab tests e.g., CBC, med blood levels, CT/MRI, EEG</td>
<td>Assess level of care &amp; supervision available</td>
</tr>
<tr>
<td>Psychodynamic signif. of neuropsychiatric sxs., disability and treatments</td>
<td>Medication allergies</td>
<td>Assess rehab needs &amp; progress</td>
</tr>
</tbody>
</table>
# Neuropsychiatric Evaluation and Treatment: Follow-up

<table>
<thead>
<tr>
<th><strong>Psychiatric</strong></th>
<th><strong>Neurologic/Medical</strong></th>
<th><strong>Social</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent pharmacologic monitoring</td>
<td>Physical signs &amp; sxs.</td>
<td>Rehabilitation</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>Physiologic response (e.g., vital signs)</td>
<td>Maximize support system</td>
</tr>
<tr>
<td>Intermittent cognitive assessments</td>
<td>Appropriate lab tests (e.g., CBC, medication blood levels, EEG)</td>
<td></td>
</tr>
<tr>
<td>Support Groups</td>
<td></td>
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</tbody>
</table>
Neuropsychiatric History

Psychiatric symptoms may not fit DSM-IV criteria
Focus on functional impairment
Document and rate symptoms
Explore circumstances of trauma
LOC, PTA, hospitalization, medical complications
Subtle symptoms - may fail to associate with trauma
How has life changed since TBI?
Thorough review of medical and psychiatric sx.
Talk with family, friends, caregivers
Assess level of care and supervision available
Assess rehabilitation needs and progress
Neuropsychiatric Treatment

- Use Biopsychosocial Model
- Treat maximum signs and symptoms with fewest possible medications
- TBI patients more sensitive to side effects
  
  START LOW, GO SLOW

- May still need maximum doses
- Therapeutic onset may be latent
- Medications may lower seizure threshold
- Medications may slow cognitive recovery
- Monitor and document outcomes
- Few randomized, controlled trials
Seven Year Prevalence of SCID* Diagnosed Psychiatric Disorders After TBI

SCID=Structured Clinical Interview for DSM-IV

Hibbard et al., 1998
One Year Cumulative Incidence of Mood Disorders After TBI

Jorge et al., 2004
Psychiatric Illness in Adult HMO Enrollees

*Predicted proportions for a women of age 40-44 with median index month (6), median log cost and no comorbid injuries

Fann et al. 2004
Delirium

• Increased risk in patients with TBI
• Undiagnosed in 32-67% of patients
  – Often missed in both inpatient and outpatient settings
• Associated with 10-65% mortality
• Up to 25% of delirious medical patients die during hospitalization and 37% within 1-3 months of onset
• Can lead to self-injurious behavior, decreased self-management, caregiver management problems
• Associated with increased length of hospital stay and increased risk of institutional placement
• Other terms used to denote delirium: acute confusional state, intensive care unit (ICU) psychosis, metabolic encephalopathy organic brain syndrome, sundowning, toxic encephalopathy
Delirium

• **Identify and correct underlying cause**
  – e.g., seizures, hydrocephalus, hygromas, hemorrhage, drug side effect or interactions, endocrine (hypothalamic, pituitary dysfunction)

• **Pharmacologic management**
  – Antipsychotics
    » haloperidol, droperidol, risperidone, olanzapine, quetiapine
  – Benzodiazepines (combined with antipsychotics)
    » lorazepam

• **Avoid polypharmacy**

• **Medical management**
  – Frequent monitoring of safety, vital signs, mental status and physical exams
  – Maintain proper nutritional, electrolyte, and fluid balance
Depression / Apathy

• Prevalence of major depression 44.3% *
  – Increased suicide risk
  – Assess pre-injury depression and alcohol use
  – Clinical presentation may vary
  – May occur acutely or post-acutely
  – May be related to neuropsychological impairment and neuroanatomical lesions
  – Associated with increased functional impairment and post-concussive symptoms

• Apathy alone - prevalence 10%
  – disinterest, disengagement, inertia, lack of motivation, lack of emotional responsivity

Prevalence of MDD after TBI

Outpatient/Referral Cases
- 42% 2.5 years post-TBI (Kreutzer et al, 2001)
- 54% average of 33 months post-TBI (Fann et al, 1995)

Unselected/Consecutive Cases
- 33-42% within 1 yr (Jorge et al, 1993, 2004)
- 13% mostly mild TBI at 1 yr (Deb et al., 1999)
- 17% mild-mod TBI at 3 mos (Levin et al., 2001)
- 27% TBI at 10-126 mos (Seel et al, 2003)
- 11%-27% TBI at 30-50 yrs (Holsinger 2002, Koponen 2002)

Phenomenology (Jorge et al 1993, Kreutzer et al 2001)
- Symptoms may vary depending on time post-TBI (e.g., anxiety, vegetative symptoms early)
- Fatigue, frustration, poor concentration common
## Patient Health Questionnaire - 9

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Spitzer et al. JAMA 1999
Surveillance for Depression After TBI
PHQ-9 to Screen for Depression

• Criterion Validity
• At least 5 symptoms scored at least several days (≥ 1), at least one cardinal symptom:
• Overall percent (point prevalence) meeting PHQ-9 screening criteria = 24.1

Sensitivity  .93
Specificity  .89

Positive Predictive Value  .63
Negative Predictive Value  .99

Fann, 2005
Rates of Major Depression after TBI (N=559)

Bombardier, Fann et al, unpublished

Percent of cases (N=559)

Cumulative incidence (53%)
Prevalence
Incidence

Months after traumatic brain injury
Major Depression by Psychiatric Hx

Cumulative Incidence

Logrank p < .001

Month

No Hx of Depression
Hx of Depression
Major Depression by Coma Severity

Cumulative Incidence

Logrank p = .833

Month

GCS 13-15
GCS 9-12
GCS 3-8
Proportion endorsing *fair to poor health* (SF-1) by MDD status (N=471)
Impact of Depression on Outcomes

Depression after TBI contributes to:

• **Poorer cognitive functioning** (Rappoport et al., 2005)

• **Lower health status and greater functional disability** (Christensen et al., 1994; Levin et al. 2001; Fann et al., 1995; Hibbard et al., 2004; Rapoport et al., 2003)

• **Poorer recovery** (Mooney et al., 2005)

• **More post-concussive symptoms** (Fann et al., 1995; Rapoport et al., 2005)
Impact of Depression on Outcomes

Depression after TBI contributes to:

- increased aggressive behavior and anxiety (Tateno et al., 2003; Jorge et al., 2004; Fann et al., 1995)
- significantly higher rates of suicidal plans (Kishi et al., 2001)
- 8 times more attempts (Silver et al., 2001)
- 3-4 times more completed suicide than in the general population and non-brain injured controls (Teasdale and Engberg, 2001)
Depression / Apathy

- Selective serotonin re-uptake inhibitors (SSRIs)
  - sertraline, paroxetine, fluoxetine
  - citalopram, escitalopram
  - venlafaxine, duloxetine (may help with pain)
- bupropion (may decrease seizure threshold)
- nefazodone (may be too sedating, liver toxicity)
- mirtazapine (may be too sedating)
- Tricyclics: nortriptyline, desipramine (blood levels)
- methylphenidate, dextroamphetamine
- Electroconvulsive Therapy – consider less frequent, nondominant unilateral

- Apathy: Dopaminergic agents - methylpyphenidate, pemoline, bupropion, amantadine, bromocriptine, modafinil
Pilot study of sertraline (N=15) (Hamilton Depression Scale-17 item)

Fann et al. 2000
Hopkins Symptom Checklist (SCL-90-R)

all p<.05
Mania

- Prevalence of Bipolar Disorder 4.2% *
- High rate of irritability, “emotional incontinence”
- May be associated with epileptiform activity
- Potential interaction of genetic loading, right hemisphere lesions, and anterior subcortical atrophy

Mania

- **Acute**
  - Benzodiazepines
  - Antipsychotics
    » olanzapine, risperidone, clozapine, others
  - Anticonvulsants
    » valproate
  - Electroconvulsive Therapy

- **Chronic**
  - valproate
  - carbamazepine
  - lamotrigine
  - lithium carbonate (neurotoxicity)
  - gabapentin, topiramate (adjunctive treatments)
Anxiety

• Often comorbid with and prolongs course of depression

• Posttraumatic Stress Disorder: Prevalence 14.1% *
  – Reexperience, Avoidance, Hyperarousal
  – > 1 month, causes significant distress or impairment
  – Possibly more prevalent in mild TBI

• Panic Disorder: Prevalence 9.2% *

• Generalized Anxiety Disorder: Prevalence 9.1% *

• Obsessive-Compulsive Disorder: Prevalence 6.4% *

Anxiety

• Benzodiazepines:
  – e.g., clonazepam, lorazepam, alprazolam
  – Watch for cognitive impairment, dependence

• Buspirone (for Generalized Anxiety Disorder)

• Antidepressants
  – SSRIs, venlafaxine, nefazodone, mirtazapine, TCAs

• Beta-blockers, verapamil, clonidine

• Anticonvulsants: valproate & gabapentin have some anxiolytic effects

• Psychosocial
  – Individual, couples, family, group
Psychosis

• Immediate or latent onset
• Symptoms may resemble schizophrenia: prevalence 0.7% *
• Schizophrenics have increased risk of TBI pre-dating psychosis
• Patients developing schizophrenic-like psychosis over 15-20 years is 0.7-9.8%
• Look for epileptiform activity and temporal lobe lesions

Psychosis

- **Antipsychotics**
  - **First generation**: e.g. haloperidol, chlorpromazine
  - **Second generation**: e.g., risperidone
  - **Third generation**: e.g., olanzapine, quetiapine, ziprasidone, aripiprazole, clozapine (seizures)

- Start with low doses

- TBI pts have high risk of anticholinergic and extrapyramidal side effects

- May cause QTc prolongation

- Use sparingly - may impede neuronal recovery acutely (from animal data)
Cognitive Impairment

• Common problems
  – Concentration and attention
  – Memory
  – Speed of information processing
  – Mental flexibility
  – Executive functioning
  – Neurolinguistic

• Association with Alzheimer’s Disease suggested

• May be associated with other psychiatric syndromes (e.g., depression, anxiety, psychosis)
  – treating these may improve cognition
# Cognitive Impairment

<table>
<thead>
<tr>
<th>May accelerate recovery</th>
<th>May impede recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>amphetamine</td>
<td>haloperidol</td>
</tr>
<tr>
<td>Norepinephrine (TCAs)</td>
<td>phenothiazines</td>
</tr>
<tr>
<td>gangliosides</td>
<td>prazosin</td>
</tr>
<tr>
<td>methylphenidate, dextroamphetamine</td>
<td>clonidine</td>
</tr>
<tr>
<td>amantadine</td>
<td>phenoxybenzamine</td>
</tr>
<tr>
<td>L-dopa/carbidopa</td>
<td>GABA</td>
</tr>
<tr>
<td>bromocriptine</td>
<td>benzodiazepines</td>
</tr>
<tr>
<td>pergolide</td>
<td>phenytoin</td>
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<tr>
<td>physostigmine</td>
<td>phenobarbital</td>
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<tr>
<td>donepezil</td>
<td>idazoxan</td>
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<tr>
<td>selegilene</td>
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<tr>
<td>apomorphine</td>
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<tr>
<td>caffeine</td>
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<tr>
<td>phenylpropanolamine</td>
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<tr>
<td>Naltrexone</td>
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<tr>
<td>atomoxetine</td>
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</table>
Aggression, Irritability, Impulsivity

• Up to 70% within 1 year of TBI
• May last over 10-15 years
• Interview family and caregivers
• Characteristic features
  – Reactive - Explosive
  – Non-reflective - Periodic
  – Non-purposeful - Ego-dystonic
• Treat other underlying etiologies (e.g., bipolar)
• Also use behavioral interventions
Manifestations of Impulsivity and Aggression

- Emotional lability
- Pathologic laughing and crying
- Rage and aggression
- Altered sexual behavior
- Lack of concern over consequences of actions
- Social indifference
- Inappropriate joking and punning
- Superficiality of emotions
Aggression, Agitation, Impulsivity (none FDA approved for this indication)

- **Acute**
  - Antipsychotics
  - Benzodiazepines

- **Chronic**
  - *Beta-blockers* (e.g., propranolol, pindolol, nadolol)
  - *Valproate, carbamazepine, gabapentin*
  - Lithium (narrow therapeutic window)
  - Buspirone
  - Serotonergic antidepressants (e.g., SSRIs, trazodone)
  - Antipsychotics (esp. second and third generation)
  - Amantadine, bromocriptine, bupropion
  - Clonidine, methylphenidate, naltrexone, estrogen

* Has most evidence for efficacy
Pilot study of sertraline (N=15) Brief Anger / Aggression Questionnaire (BAAQ)

Fann et al. Psychosomatics 2001; 42:48-54
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Depressed (n=10)</th>
<th>Non-depressed (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>50%</td>
<td>27%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>40</td>
<td>32</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>Bothered by Noise</td>
<td>50</td>
<td>32</td>
</tr>
<tr>
<td>Bothered by Light</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Loss of Temper Easily</td>
<td>70</td>
<td>32</td>
</tr>
<tr>
<td>Memory Difficulties</td>
<td>70</td>
<td>55</td>
</tr>
<tr>
<td>Fatigue</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Trouble Concentrating</td>
<td>60</td>
<td>41</td>
</tr>
<tr>
<td>Irritability</td>
<td>80</td>
<td>32</td>
</tr>
<tr>
<td>Anxiety</td>
<td>90</td>
<td>32</td>
</tr>
<tr>
<td>Sleep Disturbance</td>
<td>60</td>
<td>27</td>
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</table>
Number of Postconcussive Symptoms

<table>
<thead>
<tr>
<th># of symptoms</th>
<th>All symptoms *</th>
<th>Depressive symptoms excluded</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Current Depression</td>
<td>No current Depression</td>
</tr>
<tr>
<td>0</td>
<td>7</td>
<td>3.5</td>
</tr>
<tr>
<td>1</td>
<td>3.9</td>
<td>3.5</td>
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<tr>
<td>2</td>
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<td>3.5</td>
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<tr>
<td>3</td>
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<tr>
<td>6</td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>3.5</td>
</tr>
</tbody>
</table>

* p=.05

* p=.05
PCS – Depression Study
(Baseline and Week 8)

** Headache
Dizziness
Blurred Vision
Bothered by Noise
Bothered by Light
Loss of Temper
** Fatigue
Trouble Concentrating
* Irritability
* Memory Difficulties
Anxiety
* Sleep Disturbance

* p<.05
** p<.01
Conclusions

- Neuropsychiatric syndromes are common after TBI
- They can present in many different ways
- They can significantly increase distress, disability, and health care utilization
- Use biopsychosocial and multidisciplinary approach
- Treat as many symptoms with as few medications as possible
- Monitor systematically and longitudinally
Proposed Model

TBI

Psychiatric Vulnerability

+/-

Postconcussive Symptoms

+/-

Psychiatric Symptoms

+/-

Cognition

Correlates w/ TBI Severity?

+,-

Functioning/ QOL

Health Care Utilization