Traumatic Brain Injury: A Neuropsychiatric Perspective

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Goals and Objectives

At the conclusion of this lecture, participants will:

1. Understand the diagnostic criteria for traumatic brain injury (TBI)

2. Identify variables that affect outcome following TBI

3. Recognize the common neuropsychiatric symptoms that follow TBI

4. Be able to apply treatments for the neuropsychiatric sequelae of TBI
Case Example - 1

Ms A. is a previously healthy 34-year old, right-handed woman who sustained a mild TBI (duration of post-traumatic amnesia of ~ 2 hours) in a motor vehicle accident 2 years prior to consultation. Her Glasgow Coma Score (GCS) = 15 in the ED. She was evaluated and released into the care of her husband on the day of injury.

Since the accident she has experienced impairment in attention and memory, and has not able to work full-time as a result of these problems.

Additionally, developed problems with impulse control and affect regulation (brief paroxysms of crying and irritability).

She was prescribed buspirone 10 mg twice daily by her psychiatrist to improve impulsivity and affective lability, which she describes as moderately effective.
Case Example - 1

On interview, she describes her attention problems as most evident in her difficulty completing tasks at both work and home, such as reading lengthy pieces of information or writing notes, learning new information such as names or telephone numbers, and following conversations. These problems were especially evident (and made much worse by) noisy environments.

Neurological examination was normal.

MMSE score was 30/30.

On neuropsychological testing, she demonstrated slow but errorless performance on the Trail Making Test – Part B and a few errors of omission on the Digit Vigilance task.

Magnetic resonance imaging of the brain (clinical study) was read as “normal for age.”
Case Example - 2

A 22 year old man with no known medical, neurological, or psychiatric problems is brought to the emergency room after a motor vehicle accident.

Paramedics report that at the scene of the accident, the patient had a Glasgow Coma Scale (GCS) score of 11, but that en route to the hospital he had deteriorated rapidly from a cognitive and behavioral standpoint.

His GCS is now 5, and his blood alcohol level is found to be above the legal limit.

There is no other evidence of skull fracture, significant facial injury, or multitrauma, although he has a few rib fractures. He is intubated upon arrival to the emergency room.
Case Example - 2

A CT scan of the brain is performed immediately upon his arrival, and demonstrates a large left frontotemporal epidural hematoma, bilateral frontal and anterior temporal cortical contusions and punctate hemorrhages at the gray-white junctions, and hypodensities in the frontal white matter bilaterally.

The epidural hematoma is evacuated by the neurosurgeons within the first hour of hospitalization, but the patient remains in coma for the next seven days (day 7 GCS = 6).

He gradually emerges from coma over the following seven days (day 14 GCS = 13), although his Galveston Orientation and Amnesia Test (GOAT) scores remain in the 30-40 range.

He is evaluated by a rehabilitation team, and transferred to a neurorehabilitation unit approximately three weeks after his injury, at which time his GOAT scores remain in the 30-40 range.

At one-year post-TBI, he remains severely impaired cognitively, has frequent episodes of agitation/aggression, and experiences once-monthly partial complex seizures that intermittently generalize. He has not been able to return to work, and requires supervision from his parents for most higher-level activities of daily living.
General Definition of TBI

- Application to the brain of an external physical force or rapid acceleration and/or deceleration forces
  - not due to congenital, degenerative, vascular, hypoxic-ischemic, neoplastic, toxic-metabolic, infectious, or other causes

- Produces an immediately apparent physiological disruption of brain function manifested by cognitive or neurological impairments

- Results in partial or total functional disability (regardless of the duration of such disability)

American Congress of Rehabilitation Medicine
Definition of Mild TBI:

A traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

- any period of loss of consciousness (LOC)
- any loss of memory for events immediately before or after the accident (posttraumatic amnesia, PTA)
- any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused)
- focal neurologic deficit(s) that may or may not be transient

American Congress of Rehabilitation Medicine
Definition of Mild TBI:

- The severity of the injury does not exceed the following:
  - LOC ≤ 30 minutes
  - after 30 minutes, Glasgow Coma Scale = 13-15
  - PTA ≤ 24 hours

TBI producing disturbances that exceed these criteria is classified as moderate or severe

Self-diagnosis of TBI

- Diagnosis of TBI based on unsubstantiated claims of injury must be regarded with caution
  - under-reporting vs. over-reporting
  - poor understanding of TBI
  - misunderstanding symptoms as reflective of TBI when other diagnoses offer better explanations
  - stigma vs. secondary gains
Powell et al. 2008 (Arch Phys Med Rehabil)

- Used CDC/ACRM definition of mild TBI to screen 197 patients presenting to the ED with history or event suggestive of mild TBI

- 56% percent of mild TBI cases identified by study personnel did not have a documented mild TBI-related diagnosis in the ED record
  - lack documented diagnosis despite patients reporting findings consistent with a mild TBI diagnosis when interviewed by study personnel
Self-diagnosis of TBI

Claims of mild TBI without evidence in the medical record require careful evaluation of the history and other available evidence

- use ACRM definition of mild TBI as an anchor for the clinical history
- interview witnesses, if any, to the purported injury
- review medical, neurological, and neuropsychological evaluations (including comparison to pre-injury whenever such data can be obtained)
- review (by visual inspection, not just reports) any structural neuroimaging (CT, MRI) for findings consistent with traumatic brain injury
TBI: The Scope of the Problem

Conservative estimate: 240,000 new TBI per year

- based on CDC surveillance of TBIs resulting in hospital stay ≥ 24 hours

- only 1 in 5 patients experiencing a mild TBI are hospitalized ≥ 24 hours

Estimated actual frequencies of between 1 and 2 million new injuries per year

3.17 million Americans (1.1% of the US population) currently live with disabilities resulting from TBI

(Thurman et al. 1999; Thurman and Guerrero 1999; Marr and Coronado 2002; Zaloshnja et al. 2008)
Annual Costs of TBI

- 50,000 people in the U.S. die each year as a result of TBI
- Every year, at least 80,000 people in the U.S. develop permanent functional disabilities as a result of TBI
- Total direct cost for TBI at all levels of severity is estimated at $48.3 billion annually
  - indirect costs (e.g., lost wages by survivor and family) additive to these costs

(CDC 2001; Kraus and Sorenson 1994, Max et al. 1991)
In order to understand the effects of brain injury, we must undertake full study of the individual’s constitution. In other words, it is not just the kind of injury that matters, but the kind of brain that is injured.

Sir Charles Symonds, c. 1937
A Model of Influences on Neurobehavioral Outcome after TBI

Pre-Injury Factors

Traumatic Brain Injury

Post-Injury Psychosocial Factors

Cognitive Disturbance

Emotional Disturbance

Behavioral Disturbance

Physical Disturbance

Disturbed Consciousness
Impaired Attention
Slowed Processing
Working Memory Problems
Memory Disturbance
Functional Communication Impairments
Executive Dysfunction
Depression
Anxiety
Irritability/Lability
Rage
Agitation
Aggression
Disinhibition
Apathy
Sleep Disturbance
Headaches
Pain
Visual Problems
Dizziness/Vertigo
Seizures

(Aadapted from Silver and Arciniegas 2006)
Pre-Injury Factors

- Age and gender
- Baseline intellectual function
- Psychiatric problems & substance abuse
- Sociopathy
- “Risk-taking” and “novelty-seeking” behavior
- Premorbid behavioral problems
- Social circumstances and SES
- Neurogenetic (ie, APOE-4, COMT, ?other)
Rates of TBI-related hospitalization and death by age group as reported through the CDC TBI surveillance program in 1994 by AZ, CO, MN, MO, NY (excluding NYC), OK, and SC. Source: Thurman et al. 1999
## Pre-injury Factors

**Pre-injury psychiatric problems**

<table>
<thead>
<tr>
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<th>Pre TBI¹</th>
<th>Post TBI¹</th>
<th>Community²</th>
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<tr>
<td>Major Dep.</td>
<td>17%</td>
<td>58%</td>
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<tr>
<td>S/U Disorder</td>
<td>38%</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>PTSD</td>
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</tr>
<tr>
<td>Phobias</td>
<td>4%</td>
<td>6%</td>
<td>13%</td>
</tr>
</tbody>
</table>

¹Hibbard, Silver, et al. 2001; ²Bourdon et al. 1992
Pre-injury Factors

- Pre-injury sociopathy
- “Risk-taking” and “novelty-seeking” behavior
- Pre-injury behavioral problems (children)
  - all are complex issues with respect to outcome

Simplistically, if one has impaired impulse control, a tendency to aggression or socially inappropriate behavior, or other severe behavioral disturbances, TBI will rarely result in improvement in those problems
Neurogenetics

- An emerging approach to understanding TBI outcome
- The apolipoprotein E (APOE) genes appear to strongly influence recovery following TBI at all levels of severity
  - the APOE-4 gene negatively affects cognitive, motor, and functional outcome after TBI
- Genes that affect the metabolism of neurotransmitters in the brain and/or neuronal plasticity may influence cognitive and behavioral outcome after TBI
  - catechol-O-methyltransferase (COMT), dopamine receptor type 2 (DRD2), Taq1, ? others

Injury Factors

- **Biomechanical Injury**
  - acceleration/deceleration
  - translational/rotational
  - angular acceleration/deceleration
  - cavitation ("microexplosive")
  - diffuse axonal injury (DAI)

- **Cytotoxic Injury**
  - cytoskeletal & axonal injury
  - disturbance of cell metabolism
  - Ca$^{++}$ and Mg$^{++}$ dysregulation
  - free radical release
  - neurotransmitter excitotoxicity

- **Secondary Injury**
  - traumatic hematomas
  - cerebral edema
  - hydrocephalus
  - increased intracranial pressure (ICP)
  - systemic complications
    - hypoxia/hypercapnia
    - anemia
    - electrolyte disturbance
    - infection

Injury Factors: Translation, Rotation, & Angular Acceleration Forces

Figure adapted from Arciniegas and Beresford 2001
FLAIR MRI of the brain in a 27-year old man with a remote history of severe TBI
Severe Focal Shearing Injury → Hemorrhage → Porencephalic Cyst

T1-weighted MRI of the brain in a 44-year old man with a remote history of severe TBI
Diffuse (Multifocal) Axonal Injury

T1-weighted coronal images in a 55-year old man who suffered a severe TBI after being hit by a bus.
Figure 5. Skull base. The skull cap has been removed, exposing the inner surface of the ventral base of the skull, with the various anatomic structures with the three cranial fossa clearly defined. The uneven surface of each fossa is clearly observable. The general location of the hippocampus (medial wall of the middle cranial fossa) and where the base of the frontal lobe is located (anterior cranial fossa) are depicted. A = frontal crest; B = anterior cranial fossa; C = crista galli with cribiform plate beneath; D = sphenoid bone; E = petrous temporal bone; F = clinoid bone and area of the sella turcica; G = clivus; H = foramen magnum; I = middle cranial fossa; J = posterior cranial fossa.
Typical Locations of Cortical Contusion after Severe TBI

Coureville 1937; image courtesy of Thomas W. McAllister, MD (Dartmouth-Hitchcock Medical Center)

Coureville 1950 and Gurdjian 1975; adapted from Bigler 2007
Injury Factors: Cytotoxic Cascade

Injury Factors: Neurochemistry

- Neurotransmitter “storm” at time of TBI
  - acute increases in glutamate\(^{1-5}\), dopamine\(^{6,7}\), norepinephrine\(^{6,7}\), serotonin\(^{6-9}\), and acetylcholine\(^{10}\) are reported from CSF samples in the acute post-injury period among persons with severe TBI
  - these acute neurotransmitter excesses are functionally disruptive
  - among those who survive their injuries, cerebral glutamate, dopamine, norepinephrine, and serotonin levels appear to normalize in the days to weeks following TBI \(^{6; 11-13}\)

Injury Factors: Neurochemistry

- Persistent damage in and dysfunction of areas with dense glutamate and acetylcholine inputs

- Chronic primary cortical cholinergic dysfunction
  - damage to cerebral cholinergic nuclei (1-3)
  - loss of cholinergic afferents (3,4)
  - dysfunction of cholinergically-dependent information processing circuits (5-8)

- Possible chronic primary or secondary dysfunction in serotonin-, dopamine-, norepinephrine-dependent neuropsychiatric functions (9)

Injury Factors

- **Biomechanical Injury**
  - acceleration/deceleration
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- **Cytotoxic Injury**
  - cytoskeletal & axonal injury
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- **Secondary Injury**
  - traumatic hematomas
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    - hypoxia/hypercapnia
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    - electrolyte disturbance
    - infection

Regional Vulnerability to TBI

Yeates et al. 2007

Salmond et al. 2005

Kraus et al. 2007
Dorsolateral prefrontal cortex (executive function, including sustained and complex attention, memory retrieval, abstraction, judgement, insight, problem solving)

Orbitofrontal cortex (emotional and social responding)

Anterior temporal cortex (memory retrieval, sensory-limbic integration)

Amygdala (emotional learning and conditioning, including fear/anxiety)

Ventral brainstem (arousal, ascending activation of diencephalic, subcortical, and cortical structures)

Hippocampal-Entorhinal Complex (declarative memory)

(Figure adapted from Arciniegas and Beresford 2001)
Post-injury Factors

- Untoward medical complications
- Failure to receive timely medical, neurological, psychiatric, or other needed rehabilitative services
  - early engagement in neurorehabilitation is associated with improved functional outcomes
- Lack of education regarding the course of recovery and interpretation of symptoms
- Lack of family, friends, or resources to support recovery
- Premature return to work/school with ensuing failure to perform at expected levels
- Poor adjustment to or coping with disability by injured person or family
- Litigation or other legal entanglements
Typical Recovery Trajectories after TBI

Arciniega and McAllister 2008; Povlishock and Katz 2005; Figure adapted from: [http://www1.va.gov/vhi/docs/TBI.pdf](http://www1.va.gov/vhi/docs/TBI.pdf)
Recovery after Moderate-to-Severe TBI: Posttraumatic Encephalopathy

Stage I: Posttraumatic Coma
- profound disturbance of arousal is most salient feature
- with emergence into a state of ‘wakefulness without awareness’ (vegetative state) and ‘wakefulness with awareness’ (minimally conscious state), profound impairments in attention, processing speed, and all higher cognitive functions become obvious

Stage II: Posttraumatic Delirium (PTD)
- profound disturbance of selective and sustained attention (“reduced clarity of awareness of the environment”) with fluctuation of this and related cognitive and behavioral disturbances are most salient clinical features
- processing speed, memory, functional communication, and executive impairments are also present

(Arciniegas and McAllister 2008)
Recovery after Moderate-to-Severe TBI: Posttraumatic Encephalopathy

Stage III: Posttraumatic Amnesia (PTA)
- impairment in declarative new learning (memory) is the most salient clinical feature
- impairments in processing speed, executive function (including executive control of attention, memory, and functional communication) are also usually evident

Stage IV: Posttraumatic Executive Impairments
- impairment in executive function (including executive control of attention, memory, and functional communication) is the most salient clinical feature
- many persons also continue to experience problems with processing speed and efficiency as well

(Arciniegas and McAllister 2008)
Recovery from Moderate-to-Severe TBI

About 35-60% of persons with moderate to severe TBI will develop chronic neurobehavioral and/or physical symptoms related to TBI

- more severe initial injury increases the likelihood of incomplete neurological, neurobehavioral, and functional recovery

Successful return to work and/or school is inversely related to the severity of persistent neurobehavioral and physical symptoms
Recovery from Mild TBI

1\textsuperscript{st} week post-TBI: 90\% (or more) endorse postconcussive symptoms

1 month post-TBI: \sim 50\% are recovered fully

3 months post-TBI: \sim 66\% are recovered fully

6-12 months post-TBI: \sim 10\% still symptomatic

Those who remain symptomatic at 12 months are likely to continue experiencing postconcussive symptoms thereafter
Recovery from Mild TBI

Persistent symptoms following mild TBI are more common among persons whose injuries are in fact not “mild” at all

- mild TBI (GCS 13-15) with skull fracture, cerebral contusion, or intracranial hemorrhage (“complicated mild TBI”)
  
- mild TBI with negative neurogenetic factors (APOE-4)

Persistent symptoms following mild TBI are also more common among individuals with other significant pre-injury vulnerabilities or post-injury medical or psychosocial complications
A Model of Influences on Neurobehavioral Outcome after TBI

Pre-Injury Factors

Cognitive Disturbance

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Physical Disturbance

Traumatic Brain Injury

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Dizziness/Vertigo
Seizures

(Adapted from Silver and Arciniegas 2006)
Prevention is Essential!
Pre-Treatment Assessment

Reevaluate current treatment
- Other treatments not properly applied
- Misdiagnosis
- Poor communication among professionals

Key issues
- Indications of all drugs
- Are they still necessary?
- Potential side effects of medications
Pre-Treatment Assessment

Eliminate or at least reduce doses of neurobehaviorally problematic medications

- neuroleptics/typical antipsychotics
- benzodiazepines
- strongly anticholinergic medications
  - including some tricyclic antidepressants and paroxetine
  - phenytoin and carbamazepine
- $\alpha_2$ agonists (e.g., clonidine)
- high-dose opiates
- alcohol and other substances of abuse

(Goldstein 1999; Goldstein 2003; Stanislav 1997; Rao et al. 1985; Riches and Brown 1986; Brailowsky et al. 1986; Schallert 1986; Buffett-Jerrot and Stewart 2002; Bleigberg et al. 1993; Dixon et al. 1994; Dixon et al. 1995; Sajja et al. 1988; Smith et al. 1994; Dikmen 1991; Dikmen et al. 2000; Schierhout and Roberts 2001; Marion et al. 2006; reviewed in Arciniegas and Silver 2006)
Dopamine and Norepinephrine Antagonism

- In animal models, dopamine and norepinephrine antagonists delay neuronal recovery and neural plasticity\(^1,2\)

- Among humans, typical antipsychotics exacerbate cognitive impairments among persons with TBI\(^2,3\)
  - haloperidol increases duration of PTA following severe TBI in humans\(^4\) and in animals\(^5\)
  - risperidone increases duration of PTA and motor impairments in animals\(^5\)

- TBI increases the risk for haloperidol-induced NMS, especially with high-dose parental administration\(^6\)

Benzodiazepines

In animal models, administration of benzodiazepines suppresses induction of LTP (neural mechanism for new learning) and increases motor and sensory impairments\(^1,2,3\).

Among humans, benzodiazepines worsen motor and memory function among healthy individuals\(^4\) and persons with TBI\(^5\).

Anticholinergic Agents

In animal models of TBI, administration of scopolamine impairs memory function, even in animals with apparently recovered function\(^1,2,3\)

Among humans with TBI, anticholinergic agents (including antidepressants with potent anticholinergic properties) impair memory and other cholinergically-dependent neurobehavioral functions\(^4\)

Anticonvulsants

Double-blind, placebo-controlled trials of phenytoin\(^1,2,3\), carbamazepine\(^2\), and valproate\(^3\), among persons with TBI demonstrate:

- impaired cognition
- impaired motor function
- no benefit on the prevention of late seizures (i.e., seizures occurring after the first week post-injury)\(^1-5\)
- if an anticonvulsant must be used, valproate appears to preferable to phenytoin or carbamazepine with respect to its effects on cognition

Pre-Treatment Assessment

- Neuroimaging evaluation may be a helpful guide to treatment selection and response expectations
  - severe focal cortical and white matter damage bodes poorly for response to treatments attempting to remediate neurobehavioral deficits served by the damaged area(s)
  - diffuse axonal injury is a better prognostic finding with respect to the potential benefits of treatment
  - although "normal" conventional neuroimaging studies do not indicate that the brain is in fact uninjured, they do suggest that underlying injury may be of a sufficiently mild severity to bode well for treatment response
Treatment of Neuropsychiatric Sequelae of TBI

- Acute management focuses on reduction of symptoms interfering with rehabilitation or posing risk of harm
  - reduce risk of re-injury (setting, medications, assistive devices, etc.)

- Select patients for formal rehabilitation
  - evaluation of functional deficits and development of compensatory strategies to promote independence

- Family counseling

- Non-pharmacologic + pharmacologic treatment of acute and chronic posttraumatic neuropsychiatric problems
Nonpharmacological Treatment

- Environmental management
  - reduce overstimulation
  - facilitate adaptive engagement with the environment
  - support existing strengths and psychosocial resources

- Educational interventions for person with TBI and their families

- Symptom-targeted physical therapy, occupational therapy, speech therapy, and neuropsychological treatments (cognitive rehabilitation)\(^1,2\)

Principles of TBI Pharmacotherapy

- Define target symptoms clearly
- Therapeutic trial of all medications (pre-set dose and duration of treatment)
- Monitor side effects
- Duration of maintenance treatment
- Ease of use
- Monitor drug-drug interactions
- Augment partial responses when necessary
Posttraumatic Cognitive Impairments

In the acute and late periods following TBI, the domains of cognition most commonly affected by TBI include:

- arousal/disturbances of consciousness
- processing speed/reaction time
- attention (selective, sustained, alternating, divided)
- working memory
- memory (new learning, retrieval, or [usually] both)
- functional communication (use of language)
- executive function

(Reviewed in: Bigler 2007; Arciniegas and Silver 2006; Nuwer 2005; Meythaler et al. 2001)
Rx of Posttraumatic Cognitive Impairments

- Catecholaminergic augmentation
  - target symptoms: arousal, speed of processing, and sustained attention/vigilance
  - emerging evidence (McAllister et al. 2004) of differential effects of DA and NE on posttraumatic working memory impairments
  - additional evidence (Lipsky et al. 2002; McAllister et al. 2004) demonstrating differences in cognitive profiles and treatment response to catecholaminergic agents may be influenced by genetic polymorphisms relevant to these neurotransmitters

  - COMT, DRD2, Taq1, others?
Catecholamine Augmentation

- **Dopaminergic**
  - bromocriptine
  - carbidopa/levodopa

- **Mixed dopaminergic and noradrenergic**
  - methylphenidate
  - dextroamphetamine
  - other amphetamine salts

- **Indirect dopaminergic effects via:**
  - uncompetitive NMDA receptor antagonism
    - amantadine
    - memantine
  - ? modafinil
  - ? lamotrigine

Cholinergic Augmentation

Target symptoms: memory (encoding, retrieval, or both) and sustained attention

- in principle, arousal would be a reasonable target symptom as well

- however, the response of hypoarousal to cholinergic augmentation has not been studied in this population

Present evidence suggests that patients with posttraumatic memory impairments are most likely to benefit from this type of treatment

- among those with memory impairments who respond to cholinergic augmentation, attention and executive function may also improve
Cholinergic Augmentation: Acetylcholinesterase Inhibitors

Agents in this class of medication that have been used to treat posttraumatic cognitive impairments include:

- physostigmine
- donepezil
- rivastigmine
- galantamine

Rx of Posttraumatic Cognitive Impairments

- Catecholamine augmentation for problems with arousal, speed of processing, and perhaps sustained attention

- Cholinergic augmentation when impaired memory is the most prominent symptom
  - attention and executive function may also respond among persons with prominent memory impairments

- Both for patients inadequately responsive to either approach alone
Common Posttraumatic Emotional and Behavioral Problems

- Depression
- Mania
- Pathological Laughing and Crying
- Anxiety
- Irritability or loss of temper (“rage episodes”)
- Disinhibition
- Agitation/Aggression (“socially inappropriate behavior”)
- Apathy (loss of drive to think, feel, and/or behave)
- Psychosis
- Sleep disturbance
Depression after TBI: Epidemiology

- Most common posttraumatic mood disturbance

- Incidence: 10-77%
  - best studies suggest a range of 25-50%
  - highest rates of depression in the 1st year post-TBI

(Reviewed in Alderfer et al. 2005)
## Psychiatric Diagnoses after TBI

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<tr>
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<th>Not controlling for alcohol abuse</th>
<th>Controlling for alcohol abuse</th>
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<tr>
<td></td>
<td>Odds ratio</td>
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<td>Suicide attempt</td>
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**Table 4.** The association between psychiatric disorders and TBI after controlling for sociodemographic variables (age, sex, marital status, and SES) and quality of life variables. From the New Haven Epidemiologic Catchment Area Study (n=5034). Adapted from Silver et al. (2001).
Risk Factors for Depression after TBI

- Risk for post-TBI depression is associated with pre-injury, injury, and post-injury factors

- Pre-injury risk factors:
  - poor pre-injury occupational status
  - poor pre-morbid social function and/or poverty
  - history of psychiatric diagnosis or brain injury
  - alcohol abuse
  - fewer years of formal education
  - female gender
  - a tendency to experience high levels of stress

(Reviewed in Alderfer et al. 2005)
Risk Factors for Depression after TBI

Injury factors:

- laterality of injury (left)
  - decreased left prefrontal gray matter
  - left dorsolateral frontal and/or left basal ganglia lesions
  - proximity of injury to the left frontal pole is directly proportional to the severity of depression
- serotonergic dysfunction
- injury severity
  - higher rates of depression after mild TBI

(Lispey et al. 1983; Mobayed and Dinan 1990; Jorge et al. 1993; Glenn et al. 2001; Rapoport et al. 2002; Dikmen et al. 2004; Robinson et al. 2004)
Risk Factors for Depression after TBI

- Post-injury factors
  - Changes in autonomy
  - Altered self-image
  - Changes in close relationships (social isolation)
  - Poor psychosocial support

- Depression is also common (as high as 47%), in caregivers of persons with TBI and exposes the person with the injury to greater risk (Gillen et al. 1998)

(Reviewed in Alderfer et al. 2005)
Effects of Depression on Outcome after TBI

Posttraumatic depression is associated with other problems after TBI:

- increased suicidality
- cognitive dysfunction
- anxiety
- aggressive behavior
- poor psychosocial outcome
- increased psychosocial distress
- greater number and perceived severity of post-concussive symptoms

(Reviewed in Alderfer et al. 2005)
Effects of Depression on Outcome after TBI

- Depression interferes with physical and cognitive rehabilitation

Effective treatment of depression after TBI:

- improves depressive symptoms
- facilitates cognitive function
- reduces the number of other postconcussive symptoms
- decreases the perceived severity of remaining postconcussive symptoms

(Reviewed in Alderfer et al. 2005)
R\textsubscript{X} of Depression after TBI: SSRIs

- Selective-serotonin reuptake inhibitors (SSRIs) are highly effective and well tolerated treatment for depression following TBI:
  - present literature is strongest for sertraline
  - citalopram appears to be effective and safe
    - by extension, and in practice, escitalopram is similarly effective
  - extended half-life of fluoxetine’s primary metabolite, norfluoxetine, may present problems when side effects develop
  - anticholinergic effects of paroxetine may be problematic

(Cassidy 1989; Bessette and Peterson 1992; Wroblewski et al. 1992; Breen et al. 1997; Kant et al. 1998; Fann et al. 2000; Fann et al. 2001; Perino et al. 2001; Lee et al. 2005; Rapoport et al. 2007)
RX of Depression after TBI: TCAs

Response to tricyclic and heterocyclic antidepressants is highly variable in the TBI population

- less effective in this population vs. among persons with idiopathic (primary) major depressive disorder

- seizures in as many as 20% of patients treated with TCAs in the acute rehabilitation setting

- increased risk for cognitive impairment with higher anticholinergic load

- nonetheless, for some patients, they may be useful and reasonably well-tolerated treatments

(Saran 1985; Varney et al. 1987; Wroblewski et al. 1990; Dinan and Mobayed 1992; Wroblewski et al. 1996)
Rx of Depression after TBI: Stimulants

- Methylphenidate or dextroamphetamine may improve mood disturbances after TBI

- Best regarded as adjunctive treatments or pre-treatment to standard antidepressants

- Response of depression to a stimulant may be not only helpful symptomatically but also presage response to standard antidepressant

(Lipper and Tuchman 1976; Gualtieri and Evans 1988; Whyte et al. 1997; Lee et al. 2005)
RX of Depression after TBI: Other Antidepressants

- No published evidence to support the use of bupropion, venlafaxine, mirtazapine, duloxetine, or other newer antidepressants for posttraumatic depression

- Common clinical experience suggests that some of these agents may be useful

- Use with caution in persons with TBI given the current lack of information
  - dose-related seizure risk with bupropion merits particular concern in this population
Rx of Depression after TBI: ECT

Electroconvulsive therapy (ECT) appears to be a safe and effective treatment for severe and/or refractory post-TBI depression

- may also be useful for post-TBI mania, agitation, delirium, or psychosis
- rare increase in confusion/worsening of cognition
- no reported increase in post-traumatic seizures

Probably best reserved for use after multiple medication failures or in cases of severe, refractory, or life-threatening depression

(Ruedrich et al. 1983; Zwil et al. 1992; Crow et al. 1996; Kant et al. 1999)
Rx of Depression after TBI: Psychosocial Interventions

- Paucity of data on this aspect of treatment
- Focus on education of the injured person and his or her family
  - peer support groups increased knowledge about TBI, helped persons cope with depression better, and improved quality of life (Hibbard et al. 2002)
- A formal coping skills group intervention in a wait-list control design (Anson and Ponsford 2006)
  - improvement on the Coping Scale for Adults
  - no significant changes in anxiety, depression, self-esteem and psychosocial function
Posttraumatic Mania: Epidemiology

- Prevalence of posttraumatic mania: 2-9%
  - highest risk in the first several months post-injury
  - although the occurrence of a single manic episode merits a DSM-IV-TR bipolar disorder diagnosis, this method of diagnosis works poorly in this population

- Prevalence of posttraumatic bipolar disorder (true bi-polar presentations): uncertain, but probably <1%
Posttraumatic Mania: Epidemiology

- TBI may increase the relative risk (RR) for bipolar disorder (general population prevalence = 0.8%)
  - Van Reekum et al. (2000): 4.2% lifetime risk (RR=5)
  - Hibbard et al. (1998): 1.6% lifetime prevalence (RR=2)
  - Silver et al. (2001): Odds ratio equal in persons with and without TBI
### Psychiatric Diagnoses after TBI

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Not controlling for alcohol abuse</th>
<th>Controlling for alcohol abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Major depression</td>
<td>2.4</td>
<td>1.7-3.4</td>
</tr>
<tr>
<td>Dysthymia</td>
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<td>1.2-3.1</td>
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<tr>
<td><strong>Bipolar disorder</strong></td>
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<td><strong>0.6-3.0</strong></td>
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<tr>
<td>Obsessive-compulsive disorder</td>
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<td>1.3-3.4</td>
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<tr>
<td>Panic disorder</td>
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<td>1.5-5.2</td>
</tr>
<tr>
<td>Any phobia</td>
<td>1.7</td>
<td>1.3-2.4</td>
</tr>
<tr>
<td>Drug abuse/dependence</td>
<td>1.8</td>
<td>1.2-2.5</td>
</tr>
<tr>
<td>Alcohol abuse/dependence</td>
<td>2.2</td>
<td>1.7-2.8</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1.8</td>
<td>1.0-3.3</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>5.7</td>
<td>3.7-8.7</td>
</tr>
</tbody>
</table>

**Table 4.** The association between psychiatric disorders and TBI after controlling for sociodemographic variables (age, sex, marital status, and SES) and quality of life variables. From the New Haven Epidemiologic Catchment Area Study (n=5034). Adapted from Silver et al. (2001).

(Adapted from Silver et al., 2001)
Mania after TBI: Presentation

- The majority (>80%) of posttraumatic manias begin in the first 3 months post-TBI

- Average duration of fully symptomatic episodes of posttraumatic mania is 2 months
  - euphoric/expansive mood may persist for as long as 6 months

- Recurrence of posttraumatic mania (and development of true bi-polarity) is unusual

(Jorge et al. 1993)
Mania after TBI: Risk Factors

- Risk is not clearly related to:
  - type or severity of brain injury
  - degree of physical or intellectual impairment
  - level of social functioning
  - family/personal history of psychiatric disorder

(Jorge et al. 1993)
Mania after TBI: Risk Factors

- Risk of posttraumatic mania increased with injury to:
  - basopolar temporal lesions
  - right limbic pathways or paralimbic association cortices lesions

- Unclear association with posttraumatic seizures

(Jorge et al. 1993; Starkstein et al. 1987, 1988; Robinson et al. 1988)
A 42-year old right-handed man with no personal or family history of neuropsychiatric disorders sustained a severe motor vehicle-related TBI and developed mania about 2 months post-injury. (Figure from Oster et al. 2007)
Rx of Mania after TBI: Treatment

Very limited literature
  - case reports, case series, all open-label

Beneficial effects reported using
  - lithium (1,2)
  - carbamazepine (2,3)
  - valproate (4-7)
  - haloperidol (with or without benzodiazepines) (8)
  - quetiapine (9,10)
  - combinations of agents (3,11)

Rx of Mania after TBI: Treatment

Problems with many currently available agents when used among persons with TBI

- lithium and carbamazepine impair cognitive and motor performance among person with TBI (1-4)
- lithium lowers seizure threshold (2)
- haloperidol (and all D2 antagonists) interfere with neuronal recovery (5), cognition and motor function (6-8), and are particularly problematic when administered chronically (9)
- benzodiazepines impair cognitive and motor performance (10)

$R_X$ of Mania after TBI: Treatment

- Valproate, in most cases, is relatively neutral with respect to its effects on cognition and motor function after TBI \( (1,2) \)

- Quetiapine may improve mania and also comorbid aggression and cognitive impairment \( (3,4,5) \)

- ECT has been reported to be helpful in the treatment of posttraumatic mania \( (6) \)

Rx of Mania after TBI

- Valproate or quetiapine are probably best first-choices for posttraumatic mania
- Carbamazepine is second-line
- There is no data for lamotrigine or for any of the other atypical antipsychotics in posttraumatic mania
  - in this population, these still are probably preferable to treatment with lithium, haloperidol, or benzodiazepines
- ECT may be considered for severe or refractory posttraumatic mania
Rx of Mania after TBI

There are no published studies of psychotherapies for the treatment of posttraumatic mania

Supportive counseling and family therapy may be reasonable to employ, but their effectiveness is not presently established
Pathological Laughing and Crying

- An uncommon but potentially serious disturbance of affect regulation after TBI
  - frequency of 5-11% in the first year post-injury
  - uncertain frequency in the late period following injury

- Frequently mistaken for depression or bipolar disorder

(Zeilig et al. 1996; Tateno et al. 2004)
Pathological Laughing and Crying

A. Frequent brief episodes of involuntary and uncontrollable crying and/or laughing

B. Episodes of crying and laughing may involve an episode-congruent feeling, but do not necessarily reflect and do not produce a persistent change in the prevailing mood

C. Episodes are excessively intense with respect to the stimulus that incites them, and may be inappropriate to the context in which they develop (i.e., laughing when crying would be expected or vice versa)

D. Episodes reflect a change from usual affect regulation

E. There is evidence of an underlying neurological condition

F. The episodes are subjectively distressing and/or produce clinically significant impairments in social, occupational, or other important aspects of function

(Wortzel, Anderson, and Arciniegas 2007)
Pathological Laughing and Crying

- Although PLC may occur with depression, scores on this measure are not correlated with scores on depression measures.

- Improvement of PLC occurs independently of improvement in depression.
  
  – suggests that PLC and depression are distinct disturbances of emotional regulation.

(Schiffer et al. 1985; Robinson et al. 1993)
Lesion Location in PLC

PLC results from disinhibition or dysmodulation of pontomedullary periaqueductal gray area-tegmentum/nucleus retroambiguus complex

Lesions of the inhibitory pathways producing PLC include:

- fronto-pontine projections
- cerebello-thalamo-fronto-pontine circuit
- cerebello-pontine projections

Any brain disease impairing these circuits can produce PLC, including TBI

(Reviewed in Rabins and Arciniegas 2007 and Wortzel, Anderson, and Arciniegas 2007)
Rx of PLC

- The selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are useful treatments of PLC.

- In light of their efficacy, safety, and tolerability, SSRIs are recommended as the first-line agents for this purpose.

- Among the SSRIs, agents with short half-lives, no anticholinergic effects, and limited potential for drug-drug interactions are best suited for use among persons with TBI.
  - citalopram, escitalopram, and sertraline

(Reviewed in Wortzel, Anderson, and Arciniegas 2007)
Rx of PLC

When a TCA is used, nortriptyline, amitriptyline, and imipramine may be useful alternative treatments for PLC

– among these, nortriptyline is preferred in light of its relatively favorable side-effect profile

Catecholaminergic augmentation (e.g., methylphenidate, amantadine, levodopa) may be of benefit, but the data supporting the use of these agents for the treatment of PLC are very limited

(Reviewed in Wortzel, Anderson, and Arciniegas 2007)
Rx of PLC

- Catecholamine augmentation may be particularly useful when aimed at the concurrent treatment of posttraumatic hypoarousal, slowed processing, attention impairments, or apathy

- “Mood stabilizers” (e.g., anticonvulsants) are generally ineffective for the treatment of PLC

- Dextromethorphan/quinidine (Neurodex) may be released in the near future
  - caution when used concurrently with agents metabolized by the CYP450-2D6 pathway

(Reviewed in Wortzel, Anderson, and Arciniegas 2007)
Posttraumatic Apathy

- Apathy refers to a neurologically-determined state of diminished goal-directed cognition, emotion, and behavior
  - diminished ‘motivation’ in this context does not carry the forensic connotation of poor effort or malingering

- The syndrome of apathy reflects injury (usually bilateral) to the anterior cingulate-subcortical circuit

- Frequency of posttraumatic apathy is poorly described
  - more common among persons with severe TBI

(Kant et al. 1998; Anderson et al. 1999)
Posttraumatic Apathy

- Distinguishing between apathy and depression, where possible, is essential
  - depression: a state of persistent and excessive sadness
  - apathy: absence of goal-directed emotion, behavior, and cognition

- Many agents that improve depression (e.g., SSRIs, TCAs) worsen apathy

- However, agents that improve apathy may also improve depression
Posttraumatic Apathy

Apathy may co-occur with impulsivity and aggression.

The combination reflects concurrent injury to the anterior cingulate-subcortical combined with injury to the lateral orbitofrontal-subcortical circuit.

This is a difficult combination to treat pharmacologically:

- agents that improve apathy may worsen impulsivity and aggression, and vice versa.
Rx of Posttraumatic Apathy

- Non-pharmacologic interventions are first-line treatments of apathy
  - verbal cueing
  - environmental facilitation of activity
  - guided and/or hands-on facilitation of activity

(Silver and Arciniega 2006)
Rx of Posttraumatic Apathy

First-line: catecholaminergic augmentation
- amantadine, bromocriptine, carbidopa/L-dopa, methylphenidate, dextroamphetamine

Second-line: cholinergic augmentation
- donepezil, rivastigmine, galantamine

Third-line: activating tricyclic antidepressants
- protriptyline, desipramine, amitriptyline

Anxiety Disorders after TBI

- 20-40% in the first year after TBI
  - often comorbid with posttraumatic depression

- SSRI’s are first-line treatments

- Anticonvulsant medications (especially valproate or gabapentin) may be useful if associated with irritability, aggression, and/or pain

- Benzodiazepines are best avoided
Posttraumatic Psychosis

- Very uncommon problem (<5% lifetime risk)

- Atypical antipsychotics are first-line treatment
  - possible pro-cholinergic effect of olanzapine (via 5HT-3 and 5HT-6 antagonism) has been demonstrated to improve cognition among persons receiving this agent for the treatment of the positive symptoms (hallucinations, delusions) of schizophrenia

  - low doses preferable (avoid dose-dependent D2 receptor blockade and competitive anticholinergic effects)

- Avoid typical antipsychotics and benzodiazepines
Posttraumatic Agitation/Aggression

- Very common problem
  - up to 90% of persons with severe TBI in the acute post-injury period; frequency after mild TBI is not well described

- Atypical antipsychotics (olanzapine, quetiapine) are recommended for severe posttraumatic agitation/aggression during the acute injury period
  - quetiapine if agitation/aggression is related to or co-occurs with sleep disturbance

- Valproate is first-line therapy for non-psychotic aggression in the late post-injury period

- Avoid typical antipsychotics and benzodiazepines whenever possible
Other Neuropsychiatric Sequelae of TBI

- **Sleep disturbance**
  - low-dose trazodone (25-100 mg) is first-line
  - low-dose atypical antipsychotics (quetiapine)
  - avoid benzodiazepines and diphenhydramine

- **Fatigue**
  - treat sleep disturbances first
  - stimulants and other dopaminergically-active agents (ie, amantadine) may be of benefit
  - ? modafinil (Provigil)
Other Neuropsychiatric Sequelae of TBI

- **Headache**
  - conform to IHS headache types
  - use standard therapies
  - avoid tricyclic agents (ie, amitriptyline, or Elavil) among cognitively impaired patients

- **Epilepsy**
  - conform to ILAE seizure types
  - avoid phentoyin (Dilantin) and carbamazepine (Tegretol) among cognitively impaired patients
  - valproate (Depakote) and other newer agents with limited adverse effects on cognition are preferable
Summary

- TBI is a common and costly problem
- The neuroanatomy and neurochemistry of TBI predict substantial posttraumatic neuropsychiatric morbidity
- Post-TBI (postconcussive) neuropsychiatric symptoms can be grouped into three categories
  - cognitive
  - emotional/behavioral
  - somatic (physical)
Summary

The neuropsychiatric and functional sequelae of TBI are amenable to treatment

- early involvement (once medically stable) in neurorehabilitation improves long-term outcome

- early patient and family education as well as provision of psychosocial supports improves long-term outcome

- rational pharmacotherapy (evidence-based and/or using a priori hypotheses based on the neuroanatomy and neurochemistry of TBI) improves acute and long-term disability following TBI
No head injury is too severe to despair of, nor too trivial to ignore.

On Injuries of the Head
Hippocrates, 4th Century B.C.