Neuropsychiatric Consequences of Traumatic Brain Injury
Learning Objectives

• Explain the neuropathology associated with TBI

• Monitor for and diagnose neuropsychiatric disorders following TBI

• Optimize treatment for neuropsychiatric disorders in patients who have sustained a TBI
Anna is a 24-year-old woman who sustained a traumatic brain injury (TBI) in a motor vehicle accident 3 months ago. She has recently begun to display uncharacteristic aggressive behavior and agitation. Which of the following agents is the best choice for treating agitation and aggression in patients with TBI?

A. Diazepam
B. Propranolol
C. Haloperidol
A 16-year-old patient has recently sustained a concussion while playing hockey. Diffusion tensor imaging shows damage to white matter tracts in the patient's anterior cingulate cortex. The most likely psychiatric consequence of damage to this area is:

A. Aggression
B. Anxiety
C. Apathy
Paul is a 33-year-old veteran who sustained a mild traumatic brain injury (mTBI) during his deployment in Iraq. He has begun to show signs of pseudobulbar affect, including uncontrollable crying that does not reflect his mood. His symptoms resolve following initiation of dextromethorphan/quinidine. What is the proposed mechanism of action of dextromethorphan?

A. Sigma-1 receptor agonism  
B. NMDA antagonism  
C. Serotonin reuptake inhibition  
D. All of the above  
E. None of the above
Traumatic Brain Injury (TBI)

- Structural brain injury or physiological disruption of brain function

- Severity based on:
  - Extent of injury to the brain
  - Level of altered consciousness
  - Glasgow Coma Scale
    - Severe: <9
    - Moderate: 9-12
    - Mild: ≥13

Glasgow Coma Scale for Head Injury

<table>
<thead>
<tr>
<th>Glasgow Coma Scale, Eye opening</th>
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<tbody>
<tr>
<td>Spontaneous</td>
<td>4</td>
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<tr>
<td>To loud voice</td>
<td>3</td>
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<tr>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
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<thead>
<tr>
<th>Verbal response</th>
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<tbody>
<tr>
<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td>Confused, disoriented</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
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<tr>
<td>None</td>
<td>1</td>
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<th>Best motor response</th>
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<tbody>
<tr>
<td>Obey's</td>
<td>6</td>
</tr>
<tr>
<td>Localizes</td>
<td>5</td>
</tr>
<tr>
<td>Withdraws (flexion)</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal flexion posturing</td>
<td>3</td>
</tr>
<tr>
<td>Extension posturing</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
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Defining and Classifying TBI

• Focal damage
  – Occurs in a localized area
  – Damage to underlying tissues and vessels

• Diffuse damage
  – Widespread
  – Brain swelling, hypoxia, and diffuse axonal injury (shearing)
    • Axonal injury is a powerful predictor of morbidity and mortality

• Direct impact
  – To the head

• Indirect impact
  – To the body

• Rapid acceleration or deceleration
  – e.g., Motor vehicle accidents

• Intense pressure changes
  – Blast exposure

Patterson ZR, Holahan MR. Frontiers Cell Neurosci 2012;6(58);Epub ahead of print.
Epidemiology of Traumatic Brain Injury

• A TBI occurs every 7 seconds
• 1.7 million TBIs/year in the US
• 22% of all wounded soldiers have suffered a TBI
  – Mild TBI (mTBI) is the "signature injury" of the current military conflicts
• Underestimated?
  – Many mild injuries are likely to be overlooked
  – 25–42% of concussions go unreported
• TBI is associated with significant adverse mental health outcomes in one-third of survivors

Incidence of Sports-Related TBI

mTBI

- Mild: 80%
- Moderate: 10%
- Severe: 10%

Neuropathology of mTBI: Secondary Injury Cascades

- Stretching and shearing of axons
- Unchecked ion flux
- Ionic disequilibrium
- Release of excitatory neurotransmitters
- Overactivation of glutamate receptors
- Excitotoxicity
- Cell death
- Impaired glucose metabolism
- Impaired ATP production

Neuroinflammation Following TBI

- **Glial fibrillary acidic protein (GFAP)**
  - A measure of astrocyte activation
  - Increased as a function of brain injury severity

- **Pro-inflammatory cytokines provide defense against infection**
  - Interleukin-1 (IL-1α and IL-1β)
  - Tumor necrosis factor alpha (TNF-α)
  - Interleukin-6 (IL-6)

- **Anti-inflammatory cytokines**
  - Interleukin-6 (IL-6)
  - Interleukin-10 (IL-10)
  - Transforming growth factor beta (TGF-β)

- **Ciliary neurotrophic factor (CNF) and nerve growth factor (NGF)**
  - Promote growth and survival of neurons

Patterson ZR, Holahan MR. Frontiers Cell Neurosci 2012;6(58);Epub ahead of print.
Diffuse Axonal Injury

- Multifocal involvement of myelinated tracts
- Related to primary injury or secondary cascades
- Directly disrupts neuronal circuitry
- Degeneration and disconnection of axons may occur over several months post-injury
- Noradrenergic, dopaminergic, serotonergic, and cholinergic neurotransmitter systems may be affected
- Subsequent neuroplastic changes can lead to either favorable or maladaptive repair

Even Mild Injury Can Cause Major Problems

• Any concussion, no matter how mild, may result in permanent neurological impairment.

• Subconcussive head injuries may cause pathophysiological brain changes, including cortical dysfunction, without clinical presentation of concussion.

• Conversely, some individuals with apparently severe injuries have good functional outcomes.

• Post-concussive syndrome (PCS)
  – Constellation of ongoing physical, cognitive, and emotional symptoms associated with TBI.

Long-term Consequences

- 48.3% of patients with TBI have an incident Axis I psychiatric disorder when assessed 30 years post-injury
- As many as 33% of individuals with mTBI report persistent problems
  - Cognitive dysfunction is the most commonly reported problem
- 1.1% of the US population (~3.2 million people) has long-term disability secondary to mTBI
- Neurocognitive, psychiatric, and behavioral disturbances may not be immediately evident

Factors That Modulate Outcome After TBI

- Polymorphisms in genes that modulate response to neurotrauma
  - e.g., Key points in excitotoxic injury cascades
- Efficiency of neural repair or plasticity
- Baseline (pre-injury) cognitive and behavioral functioning
- Cognitive deficits appear to correlate with TBI severity
- Emotional symptoms do not correlate with TBI severity

Before and After TBI

- Pre-injury psychiatric disorders may increase the risk of developing post-injury psychiatric disorders
  - Not all studies show a correlation between pre-injury mental health and post-injury outcome

- Measures of emotional factors taken 3–7 days following injury are the best behavioral predictors of post-concussive syndrome at 3 months

- 41% of individuals with TBI develop a new psychiatric condition in the 3 years post-injury

- Two-thirds of cases of depression and anxiety develop for the first time post-injury

Neuroanatomy of Neuropsychiatric Symptoms Following TBI

Reticulothalamic system
- Impairments in consciousness
- Hypothalamus: Dysautonomia, thermoregulation problems, altered feeding behaviors, endocrine dysfunction, sleep-wake cycle disturbances, pathological affect

Reticulocortical system
- Hypoarousal, inattention, impaired information processing

Anterior cingulate cortex
- Apathy

Anterior cortex
- Disturbances in semantic memory, processing of social cues

Inferolateral prefrontal cortex
- Working memory impairments

Dorsolateral prefrontal cortex
- Impairments in executive function

Ventral cortex
- Disinhibition, irritability, aggression

Ventral forebrain
- Impairments in attention, memory, and executive function

Hippocampus
- Impaired sensory gating, attention, working memory

Amygdala
- Anxiety

Standard Neuroimaging

• Damage from mTBI is often not evident on CT or MRI
  – ~44% of patients with mTBI who develop 3 post-concussive syndrome symptoms show no CT abnormalities

• fMRI has potential for detecting metabolic dysfunction; still experimental at this point

Diffusion Tensor Imaging (DTI)

- Advanced form of MRI that outlines axonal tracts
- Allows detection of microstructural axonal injury

Common Psychiatric Sequelae of TBI

• TBI may make the brain vulnerable to the development of mental disorders

• Neuropsychiatric issues are more prevalent in TBI patients than the general population

• Depression and anxiety disorders are the most common diagnoses

• Associated with poorer recovery, difficulty maintaining social relationships, and unemployment

Common Psychiatric Sequelae of TBI

- 44% of individuals with TBI-related psychiatric diagnoses have 2 or more disorders
- Of veterans diagnosed with TBI:
  - Three-fourths are also diagnosed with PTSD
  - One-half are also diagnosed with depression
- Patients with major depression following TBI are 8X more likely to have comorbid anxiety compared to patients with TBI and no depression
- Symptoms (e.g., irritability, sleep disturbance) may be attributable to a psychiatric illness (e.g., PTSD, depression), TBI itself, or a combination of both
- Neuropsychiatric symptoms of patients with TBI may not fit neatly into DSM diagnostic criteria

# Depression in Patients With TBI

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Core Features</th>
<th>Neurobiological Substrates</th>
<th>Other Correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–50%</td>
<td>o Episodes of sadness</td>
<td>Lesions to left dorsolateral-frontal and/or basal ganglia regions</td>
<td>Unemployment, low income, minority status, younger age, history of alcohol dependence, and pre-TBI history of depression</td>
</tr>
<tr>
<td></td>
<td>o Negativism</td>
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<td></td>
<td>o Loss of pleasure</td>
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<td></td>
<td>o Hopelessness</td>
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<td></td>
<td>o Suicidal thoughts</td>
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<td></td>
<td>o Depressed mood often presents as irritability, frustration, anger, hostility, and aggression rather than sadness</td>
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<td>o Somatic symptoms may be absent</td>
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Depression in Patients With TBI

- Depression is the most common psychiatric complication of TBI
- Patients with TBI remain at elevated risk of depression for decades post-injury
- 90% of patients with major depressive disorder (MDD) had onset of depression post-TBI
- Patients with mTBI and depression are more likely to report loss of consciousness at the time of injury
- Depression following TBI is associated with more severe post-concussive symptoms, including headache, blurred vision, dizziness, and memory impairment

Suicide in Patients With TBI

- Suicide rates among patients with TBI are higher than in the general population
- Patients with TBI and loss of consciousness have 4X greater likelihood of attempting suicide than the general population
- 10–33% of patients report suicidal ideation 1 year post-TBI
- 15% of patients attempt suicide by 5 years post-TBI

Neurobiology of Depression Following TBI

• Dorsolateral frontal, temporal, and left basal ganglia lesions have been associated with onset of depression following TBI

• Volume deficits and axonal damage in the hippocampus, corpus callosum, basal ganglia, and dorsolateral prefrontal cortex (DLPFC) have been reported in patients with TBI and depression compared to those with TBI and no depression

• Left rostral anterior cingulate and bilateral orbitofrontal cortices have also been implicated

• Chronic neuroinflammation?
  – Microdamage activates neuroinflammation

Depression in Patients With TBI: Treatment

• In addition to improving psychosocial function and quality of life, successful treatment of depression may alleviate other post-concussive symptoms, including:
  – Anergia
  – Insomnia
  – Irritability
  – Cognitive deficits

• All antidepressants are considered off label in this population

Depression in Patients With TBI: Treatment

• SSRIs
  – First-line treatments for depression following TBI
  – Most evidence exists for sertraline and citalopram
  – Among the SSRIs, sertraline has the most dopaminergic effects
    • May improve cognition
  – Paroxetine may impair cognition due to antimuscarinic properties

• TCAs
  – Evidence for less efficacy than SSRIs
  – Higher risk of side effects, especially seizures and cognitive deficits, in patients with TBI

Depression in Patients With TBI: Treatment

- **Bupropion**
  - Not recommended (especially the immediate release formulation) because it lowers the seizure threshold

- **MAOIs**
  - Not usually recommended due to lack of efficacy data
  - Dietary restrictions may be harder to follow due to cognitive deficits in patients with TBI

- **Methylphenidate**
  - Has shown similar efficacy to sertraline in patients with TBI
  - Added benefit of improving cognitive deficits

- **Physical activity and cognitive behavioral therapy (CBT)** have shown some promise

Depression in Patients With TBI: Treatment

- Limited evidence for the efficacy and tolerability of:
  - Electroconvulsive therapy (ECT)
    - Cognitive side effects must be closely monitored
  - Low-intensity magnetic field exposure
  - Biofeedback
  - Acupuncture

Auricular Acupuncture

- "Exhaustion of Heart Fire"
  - Manifests as concentration and memory problems, anxiety, depression, and disturbed sleep

- "Stagnant Liver Qi"
  - Manifests as muscle tension, hypervigilence, irritability, and outbursts of rage

- "Kidney Yin and Yang Depletion"
  - Manifests as fatigue, fear, and helplessness

Special Considerations in Patients With TBI: Antidepressants

• Most patients with post-TBI depression do not respond to standard antidepressant therapy.

• Depression resulting from a basal ganglia lesion could potentially worsen with antidepressants.

• Bupropion and TCAs have an increased risk of seizure associated with them.

• Some antidepressants may also interfere with motor function, which may already be compromised in patients with TBI.

• Antidepressants with anticholinergic properties (e.g., paroxetine) may further impair cognition.

Mania in Patients With TBI

- Risk of bipolar disorder increases 5.3-fold following TBI
- Seizures develop in 50% of patients who develop mania following TBI

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Core Features</th>
<th>Neurobiological Substrates</th>
</tr>
</thead>
</table>
| 1–10%      | o Episodes of irritability and/or elevated mood  
             o Increased energy  
             o Impulsivity      | Lesions to temporal lobe and right orbitofrontal cortex |

- Treatment of mania in patients with TBI
  - Valproate
  - Lithium is recommended second-line due to seizure risk

## Anxiety in Patients With TBI

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Core Features</th>
<th>Neurobiological Substrates</th>
<th>Other Correlates</th>
</tr>
</thead>
</table>
| 10–70%     | o Feelings of apprehension or dread without autonomic symptoms  
o PTSD is anxiety with:  
  • Re-experiencing  
  • Avoidant behavior  
  • Emotional numbing  
  • Hypervigilence | Lesions to right hemisphere in anxious depression | PTSD is more common with mTBI |

Anxiety Disorders in Patients With TBI

• TBI increases risk of:
  – Generalized anxiety disorder by 2.3X
  – Panic disorder by 5.8X

• Prevalence rate 15 years following TBI: 44%

• Over two-thirds of anxiety disorders have onset following TBI

• In most cases, panic disorder manifests over 10 years following TBI
  – Suggests a slowly evolving reaction to injury

• Anxiety in the acute stage is a significant predictor of post-concussive syndrome

Posttraumatic Stress Disorder (PTSD) in Patients With TBI

• mTBI increases risk for development of PTSD by 5.8X

• 16.5% of patients with TBI meet diagnostic criteria for PTSD

• Of 2234 OEF/OIF veterans:
  – 12% have mTBI
  – 11% have PTSD
  – 44% of those with loss of consciousness have PTSD

• Conversely, the combat environment may independently increase the risk for both TBI and PTSD

PTSD in Patients With TBI

• Combat-related TBI may be associated with damage that predisposes an individual to PTSD
  – Common brain areas are implicated in both PTSD and post-concussive syndrome
  – Inadequate frontal inhibition of limbic structures

• Overlapping symptoms between TBI and PTSD include:
  – Concentration and recall problems
  – Sleep disturbances
  – Mood/emotional irregularities

PTSD "Pharmacy"

Only sertraline and paroxetine are FDA-approved to treat PTSD

Stahl SM. Stahl’s essential psychopharmacology. 4th ed. 2013;

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Personality Changes in Patients With TBI

• Affect one-third of patients with TBI

• Often a primary source of concern for family members, though often unrecognized by patients

• Personality changes can persist for years post-injury

• Changes include:
  – Apathy: damage to reward circuitry
  – Emotional lability: damage to frontal cortex/limbic connections
  – Impaired judgment: damage to prefrontal cortex
  – Increased impulsivity: damage to frontal cortex
  – Irritability: damage to orbitofrontal cortex

## Aggression in Patients With TBI

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<tr>
<th>Prevalence</th>
<th>Core Features</th>
<th>Neurobiological Substrates</th>
<th>Other Correlates</th>
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</thead>
<tbody>
<tr>
<td>30%</td>
<td>o Verbal outbursts</td>
<td>Frontal lobe injuries</td>
<td>Pre-injury history of substance abuse and aggressive behavior</td>
</tr>
<tr>
<td></td>
<td>o Use of profanity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Destruction of property</td>
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<tr>
<td></td>
<td>o Violent attacks on others</td>
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Aggression and Agitation in Patients With TBI

- 34% of patients with TBI exhibit aggressive behavior
- Hostility, temper outbursts, and poor self-control may be present for decades following TBI
- Risk factors for aggression following TBI
  - Frontal lobe injury
  - Premorbid affective disorder
  - Personality disorder
  - Alcohol or substance abuse
- Presence of agitation during acute recovery predicts poorer psychological adjustment and long-term outcomes

Aggression in Patients With TBI: Treatment Options

• Best evidence is for beta blockers, including propranolol

• Other options include:
  – Methylphenidate
  – Paroxetine
  – Lithium
  – Desipramine
  – Sertraline
  – Valproate
  – Amitriptyline
  – Buspirone

• Agents that cause sedation or further impair cognition should be avoided if possible

• Some evidence suggests that benzodiazepines, haloperidol, and clonidine may impair recovery
  – Benzodiazepines may actually cause paradoxical agitation in patients with TBI

Pseudobulbar Affect (PBA) in Patients With TBI

• Occurs in the context of brain injury, including TBI, stroke, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS)

• Found in 5–11% of patients with TBI

• PBA is characterized by uncontrollable, inappropriate laughing and/or crying

• Patients may experience autonomic changes, increased jaw jerk, exaggerated gag reflex, tongue weakness, dysarthria, dysphagia, and episodic proneness to anger

• Patients with PBA often have:
  – Increased risk of depression and anxiety
  – Decreased quality of life
  – Impaired social interaction (due to embarrassment)

PBA Neurobiology

• Both serotonergic and dopaminergic pathways seem to be involved
  – Glutamatergic and sigma-1 receptors may also be involved

• Hypothetically due to abnormal prefrontal modulation of hypothalamic, pontine, and medullary centers
  – These brainstem areas coordinate facial expressions

• Damage to the cerebellum or to cerebellar cortical and subcortical connections may also be involved

PBA Diagnosis

• PBA is often under-recognized, misdiagnosed, and undertreated
  – Only 40% of individuals who discuss PBA symptoms with a clinician are diagnosed

• PBA is a disorder of affect (the expression of mood), not mood itself

• Often mistaken for depression
  – Duration of PBA episode is shorter (seconds vs. weeks)
  – Crying is not congruent with subjective mood
  – Other symptoms of depression (fatigue, anhedonia, hopelessness, guilt, etc.) are not associated with PBA
  – PBA generally responds faster to pharmacotherapy

• Ictal laughing and crying can also be signs of complex partial epilepsy
  – Usually accompanied by alterations in consciousness

Pseudobulbar Affect in Patients With TBI: Treatment

• Dextromethorphan
  – Coadministered with quinidine (CYP450 2D6 inhibitor)
  – Potent sigma-1 receptor agonist
    • Sigma-1 receptors: expressed in cerebellum and brainstem
    • Modulates NMDA signaling, inhibiting presynaptic release of glutamate in cortex
    • Modulates postsynaptic intracellular Ca\(^{2+}\) mobilization
  – Uncompetitive NMDA receptor antagonist
    • Limits glutamatergic signaling and potentiates dopaminergic signaling
  – Serotonin reuptake transporter (SERT) inhibitor

Garnock-Jones KP. CNS Drugs 2011;25(5):435-45;
• Antidepressants, amantadine, and L-dopa are also used off-label – limited evidence
## Cognitive Impairment in Patients With TBI

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Core Features</th>
<th>Neurobiological Substrates</th>
<th>Other Correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–70%</td>
<td>o Inattention</td>
<td>Injury to medial temporal regions, dorsolateral prefrontal cortex, and subcortical white matter connecting these regions</td>
<td>TBI severity</td>
</tr>
<tr>
<td></td>
<td>o Difficulty learning new information</td>
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<tr>
<td></td>
<td>o Inability to process information</td>
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<td></td>
<td>o Inability to problem solve</td>
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<td></td>
<td>o Executive dysfunction</td>
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Cognitive Deficits in Patients With TBI

• Most common complaint following TBI
• Cognitive deficits persist for decades following injury
• Deficits may include decreased ability to:
  – Maintain attention
  – Inhibit incorrect responses
  – Recognize mistakes
• Attentional deficits in young adults with a history of concussion mimic those seen in older patients who are transitioning from mild cognitive impairment (MCI) to Alzheimer's disease (AD)

Cognitive Deficits in Patients With TBI: Treatment

- **Psychostimulants**
  - Augment cerebral catecholaminergic function
  - May improve processing speed, arousal, attention, and memory
  - Methylphenidate
    - Not recommended for patients with a history of substance abuse
  - Dextroamphetamine

- **Cholinesterase inhibitors**
  - Donepezil
  - Rivastigmine

- **Amantadine**
  - Not approved for this indication

Alzheimer's Disease (AD) in Patients With TBI

• TBI may initiate the molecular cascades involved in Alzheimer's disease pathology

• Damage to axons leads to impaired protein transport
  – Buildup of amyloid-beta and tau

• Apolipoprotein E epsilon 4 (APOE\(\varepsilon\)4)
  – Genetic risk factor for AD
  – Individuals who are APOE4 positive and sustain a TBI are at 10X greater risk of developing AD

• Diminished cognitive reserve associated with TBI may facilitate development of AD in susceptible individuals
Chronic Traumatic Encephalopathy (CTE)

- Described in professional athletes who have received more than 1 concussion
- Characterized by neurofibrillary tangles in frontal and temporal cortices
- Amyloid deposits may or may not be present
- Midlife behavioral and parkinsonian symptoms
  - Disordered cognition, memory loss, executive dysfunction, depression, apathy, disinhibition, irritability

AD vs. CTE

AD:
NFTs in deeper cortical layers

CTE:
NFTs in more superficial cortical layers

Chronic Traumatic Encephalopathy (CTE)

In December 2012, Boston University researchers identified four stages of CTE.

Listed below are possible symptoms by stage:

**Stage 1:** Depression, headaches, short-term memory loss

**Stage 2:** Difficulty controlling impulses, suicidal thoughts, severe headaches

**Stage 3:** Apathy, severe memory issues, impaired judgement

**Stage 4:** Paranoia, severe depression, aggression, suicidal behaviors

Concussions last more than a lifetime...

www.HeadsUpCTE.com
Recent NFL Suicides Attributed to CTE

Andre Waters 1962-2006
Dave Duerson 1960-2011
Junior Seau 1969-2012
Ray Easterling 1949-2012
Dementia Pugilistica: The CTE of Boxing

Fritzie Zivic 1913-1984
Sugar Ray Robinson 1921-1989
Jerry Quarry 1945-1999

Jimmy Young 1948-2005
Willie Pep 1922-2006
Floyd Patterson 1935-2006
Mike Quarry 1951-2006

Emile Griffith 1938-2013
Jimmy Ellis 1940-
Bobby Chacon 1951-
Wilfred Benítez 1958-
Meldrick Taylor 1966-
Psychosis in Patients With TBI

- TBI increases the risk of developing schizophrenia by 60%
  - Possibly associated with frontal and temporal lobe damage
- Delay to onset of symptoms: 4 years
- 33–58% of patients with TBI-related psychosis experience seizures
- Diagnosis may be difficult because:
  - Patients with schizophrenia may be at a higher risk of sustaining a TBI during their lifetime
  - Schizophrenia-like psychosis occurs 12X more frequently in patients with seizure disorder compared to the general population

## Psychosis in Patients With TBI

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<tr>
<th>Prevalence</th>
<th>Core Features</th>
<th>Correlates</th>
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<tbody>
<tr>
<td>3–8%</td>
<td>o Loss of touch with reality&lt;br&gt;o Disorganized thought process&lt;br&gt;o Hallucinations&lt;br&gt;o Delusions</td>
<td>TBI before adolescence and congenital neurological disorder</td>
</tr>
</tbody>
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Special Considerations in Patients With TBI: Antipsychotics

• The use of antipsychotics in patients with TBI is controversial

• May further impair cognitive deficits due to:
  – Dopamine receptor antagonism
    • May exacerbate the hypodopaminergia often caused by brain injury
  – Cholinergic properties
    • Many atypical antipsychotics bind to muscarinic receptors

Sleep Disturbances in Patients With TBI

- 72% of patients with TBI have a sleep–wake disorder
  - Excessive daytime sleepiness and fatigue: 55%
  - Insomnia: 30%
  - Circadian rhythm disorders: 36%
  - Obstructive sleep apnea and narcolepsy are also not uncommon

- Insomnia in patients with TBI is associated with headaches, depressive symptoms, and irritability

- Unrecognized or untreated sleep disorders may worsen outcomes and increase disability from TBI

Loss of Hypocretin (Orexin) Neurons Following TBI

- 27% loss of hypocretin neurons in patients with TBI
  - Hypothalamic damage

- Low hypocretin levels correlated with sleepiness at 6 months post-TBI
Sleep Disturbances in Patients With TBI: Treatment

- Sleep hygiene education
- Trazodone
- Mirtazapine

Avoid or use caution with:
- Agents with anticholinergic properties
  - Nonprescription drugs (e.g., Unisom)
  - Nortriptyline/amitriptyline
- Benzodiazepines
  - May interfere with neuroplasticity and recovery and worsen cognitive deficits
  - Antipsychotics may worsen obstructive sleep apnea

General Guidelines for Treating Patients With TBI

• Avoid agents with anticholinergic properties and agents that are sedating
  – May worsen already-impaired cognition

• Avoid agents that lower the seizure threshold
  – Individuals with TBI may already be at an increased risk for seizure activity

• Avoid conventional antipsychotics
  – Some animal data suggest poorer neuronal recovery
  – Patients with TBI may be more prone to EPS and tardive dyskinesia

• Start low and titrate slow
  – The injured brain may be more sensitive to psychototropic effects
Summary

• Individuals who sustain a TBI should be monitored regularly for the development of neuropsychiatric symptoms

• Even mild TBI significantly increases the risk of psychiatric illness, including depression, anxiety, PTSD, mania, pseudobulbar affect, and dementia

• The specific psychiatric consequences of TBI are likely dependent upon which brain areas and circuits sustain injury

• Special considerations should be taken when using psychotropic medications in patients with a history of TBI