Neuropharmacology of Traumatic Brain Injury

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Neuropsychiatric Sequelae

• Delirium
• Depression / Apathy
• Mania
• Anxiety
• Psychosis
• Cognitive Impairment
• Aggression, Agitation, Impulsivity

Neurobiological Mechanisms

• Frontal and temporal lobe lesions lead to neuropsychiatric syndromes

• Diffuse axonal injury, hypoxia, hypometabolism, free radical and excitotoxic neurotransmitter release
  – can affect serotonin, norepinephrine, dopamine, acetylcholine, and GABA systems

Examples of Neuropsychiatric Syndromes Associated with Neuroanatomical Lesions

• Lateral orbital pre-frontal cortex
  – Irritability
  – Mood lability
  – Impulsivity
  – Mania
• Anterior cingulate pre-frontal cortex
  – Apathy
  – Akinetic mutism
• Dorsolateral pre-frontal cortex
  – Poor memory search
  – Poor set-shifting / maintenance
• Temporal Lobe
  – Memory impairment
  – Psychosis
  – Mood lability
  – Aggression
• Hypothalamus
  – Sexual behavior
  – Aggression
Neuropsychiatric Evaluation and Treatment: Etiologies

<table>
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<tr>
<th>Psychiatric</th>
<th>Neurologic/Medical</th>
<th>Social</th>
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<tbody>
<tr>
<td>Premorbid</td>
<td>Neurologic illness</td>
<td>Social, family, vocation</td>
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<tr>
<td>Psych disorders &amp; sxs.</td>
<td>Lesion location, size, pathophysiology</td>
<td>Rehabilitation situation and stressors</td>
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<td>Personality traits</td>
<td>Other medical illness</td>
<td>Functional impairment</td>
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<td>Coping styles</td>
<td>Other indirect sequelae</td>
<td>Medico/legal</td>
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<tr>
<td>Substance Abuse</td>
<td>(e.g., pain, sleep disturb)</td>
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<td>Medication side effects &amp; interactions</td>
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<td>Psychodynamic signif. of neurologic illness</td>
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<tr>
<td>Family psych. history</td>
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Roy-Byrne P, Fann JR. APA Textbook of Neuropsychiatry, 1997

Neuropsychiatric Evaluation and Treatment: Workup

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

- Characterize diagnosis/symptoms as precisely as possible
  - Psychiatric symptoms may not fit DSM-5 criteria
- Focus on functional impairment
- Document and rate symptoms (use validated instruments, if available)
- Assess pre-TBI personality, coping, psychiatric history (anxiolytic use is RF for TBI (Fann et al, 2002))
- Talk with family, friends, caregivers
- How has life changed since TBI?
  - Impact on self-image, cognition, function
- Thorough review of medical and psychiatric symptoms
- Assess level of care and support available
Neuropsychiatric Treatment

- Use Biopsychosocial Approach
- Define realistic treatment endpoints
- What’s worked in the past?
- Treat maximum signs and symptoms with fewest possible medications
- TBI patients more sensitive to side effects
  - START LOW, GO SLOW, BUT GO
- May still need maximum doses
- Therapeutic onset may be latent
- Involve support system

Psychiatric Illness in Adult HMO Enrollees (N=939 with TBI, 2817 controls)

Fann et al. Arch Gen Psychiatry 2004; 61:53-61

Polypharmacy

Common Comorbidities in TBI

- Anxiety / Worry / Panic
- Depression
- Insomnia
- Pain
- Irritability / Anger
- Fatigue
Common Polypharmacy Pitfalls

- Anxiety / Worry / Panic
  - Benzodiazepines
- Depression
  - Antidepressants
- Insomnia
  - Sedative-hypnotics
- Pain
  - Opioids, gabapentin
- Irritability / Anger
  - Beta-blockers, antipsychotics
- Fatigue
  - Psychostimulant

Potential Consequences of Polypharmacy

- Drug-drug interactions
- Accidental or volitional overdose
- Non-adherence
- Cumulative adverse effects
  - E.g., sedation, lightheadedness, cognitive impairment, fatigue
- Delirium
- Accidents (falls, MVAs)
- Unnecessary health care utilization & costs

Management Opportunities

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<tr>
<th></th>
<th>Anxiety</th>
<th>Depress</th>
<th>Insomnia</th>
<th>Pain</th>
<th>Irritable / Anger</th>
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<td>(e.g., gabapentin)</td>
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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
  – TBI increases a person’s vulnerability
    – e.g., seizures, hydrocephalus, hygromas, hemorrhage, drug side effect or interactions, endocrine (hypothalamic, pituitary dysfunction), metabolic (e.g., sodium, glucose), infections
• Pharmacologic management
  – Antipsychotics
    » Haloperidol (e.g., IV), droperidol, risperidone, olanzapine, quetiapine (taper 7 – 10 days after return to baseline)
    » May cause QTc prolongation, metabolic syndrome, sudden cardiac death in elderly
  – Benzodiazepines (combined with antipsychotics), alcohol or sedative withdrawal
    » Lorazepam
• Minimize 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% *
  – Assess pre-injury depression and alcohol use
  – Use ‘inclusive’ diagnostic technique
  – May occur acutely or post-acutely
  – Not directly related to TBI severity
• Apathy alone - prevalence 10%
  – disinterest, disengagement, inertia, lack of motivation, lack of emotional responsivity

MDD & PTSD after TBI

• Army soldiers: (Hoge et al, 2008)
  – Mild TBI with LOC: 43.9% PTSD, 22.9% MDD
  – Mild TBI without LOC: 27.3% PTSD, 8.4% MDD
  – Other injuries: 16.2% PTSD, 6.6% MDD
• Civilians:
  – MDD Point prevalence 26-31%
  – MDD Period prevalence 42-53% within the first year, 61% within the first 7 years after TBI.
  – Rates of depression are not associated with TBI severity
  – Rates of PTSD following mild TBI (11-24%) are about twice as high as rates following moderate to severe TBI

Impact of Depression on Outcomes

Depression after TBI associated with:
• 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; Rappoport et al., 2003)
• More post-concussive symptoms (Fann et al, 1995; Rappoport et al., 2005)
• Increased aggressive behavior and anxiety (Tateno et al., 2003; Jorge et al., 2004; Fann et al., 1995)
• Poorer recovery and return to work (Mooney et al., 2005; Hoge et al, 2008)
• Higher rates of suicidal plans (Kah et al., 2001), 8 times more suicide attempts (Silver et al., 2001), 3-4 times more completed suicides (Tweedale and Engberg, 2001); than in non-brain injured controls
Importance of Depression & PTSD

- Hoge et al, NEJM 2008
  - Many putative mild TBI-related symptoms may overlap with and be mediated, at least in part, by depression and PTSD
    » Overall Health
    » Missed Workdays due to illness
    » Medical Visits due to physical condition
    » Somatic & post-concussive symptoms (including memory & concentration problems)

Pharmacotherapy Trials in TBI

- Systematic Review: 13 studies
- One class I study (Ashman et al., 2009), N=52
  - showed trends toward superiority of sertraline over placebo
  - temporally far removed from TBI (18 yrs)
  - underpowered to examine predictors of response
- Cannot assume standard treatments have same efficacy and tolerability in TBI
- SSRIs were the best tolerated
- 6 studies of electroconvulsive tx, acupuncture, magnetic field exposure, biofeedback

Depression / Apathy

- Selective serotonin re-uptake inhibitors (SSRIs)
  - sertraline - paroxetine - fluoxetine
  - citalopram - escitalopram
  - venlafaxine, duloxetine, levomilnacipran (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, selegiline, modafinil (no RCTs in TBI)

Pilot study of sertraline after Mild TBI (N=15)

(Hamilton Depression Scale)

Fann, Hart, Schomer, J Neurotrauma 2009

Mania

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


Pseudobulbar Affect

A neurologic condition characterized by episodes of crying or laughing that are sudden, frequent, and involuntary

Occurs in patients with TBI, MS, ALS, stroke, and certain other neurologic conditions

FDA-approved in 2011 – Nuedexta ®
  - Dextromethorphan (20mg) – modulates glutamate
  - Quinidine (10mg) – metabolic inhibitor

Mania

- Acute
  - Benzodiazepines
  - Antipsychotics
    - olanzapine, risperidone, quetiapine, clozapine
  - Anticonvulsants
    - valproate
  - Electroconvulsive Therapy
- Chronic
  - valproate
  - carbamazepine
  - lamotrigine
  - lithium carbonate (neurotoxicity)
  - gabapentin, topiramate (adjunctive treatments)
Anxiety & Related Disorders after TBI

- Often comorbid with and prolongs course of depression, substance use
- Panic Disorder: Prevalence 9.2%
- Generalized Anxiety Disorder: Prevalence 9.1%
- Obsessive-Compulsive Disorder: Prevalence 6.4%
- Posttraumatic Stress Disorder: Prevalence 14.1%
  - Intrusions, Avoidance, Cognitions/Mood, Arousal
  - >1 month, causes significant distress or impairment
  - More prevalent in mild TBI

Anxiety Mediations
- Benzodiazepines: use lower doses (~50% typical dose), taper when possible
  - e.g., clonazepam, lorazepam, alprazolam
  - Watch for cognitive impairment, disinhibition, dependence
- Buspirone (for Generalized Anxiety Disorder)
- Antidepressants: SSRIs, SNRIs, mirtazapine, TCAs, trazodone, nefazodone, MAOIs
- Beta-blockers, verapamil, clonidine
- Prazosin (for PTSD nightmares)
- Anticonvulsants: valproate, gabapentin, pregabalin, vigabatrin, tiagabine have some anxiolytic effects
- Antihistamines: hydroxyzine, diphenhydramine
- Antipsychotic augmentation: olanzapine, quetiapine, risperidone
- Psychosocial: CBT, Behavioral Activation, couples/family, group

Psychosis

- Hallucinations, delusions, thought disorder
- 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%

Psychosis

- Antipsychotics
  - First generation: e.g. haloperidol, chlorpromazine (seizures)
  - Second generation: e.g., risperidone
  - Third generation: e.g., olanzapine (2 case reports), quetiapine, ziprasidone, aripsiprazole, paliperidone, clozapine (seizures)
- Start with low doses (e.g., Risperidone 0.5mg qHS)
- TBI pts have high risk of anticholinergic and extrapyramidal side effects
- May cause QTc prolongation, increased sudden death in elderly, metabolic syndrome
- 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, insomnia) – *treatment may improve cognition*

Cognitive Impairment

May improve recovery

• Stimulants
  – methylphenidate, dextroamphetamine, caffeine
• Nonstimulant dopamine enhancers
  – amantadine, bromocriptine, pramipexole, L-dopa/carbidopa
• Acetylcholinesterase inhibitors
  – physostigmine, donepezil, rivastigmine, galantamine
• Antidepressants
  – sertraline, fluoxetine, milnacipran (SNRI)
• Others
  – Citicoline (recent negative study JAMA 2012), gangliosides, pergolide, selegiline, apomorphine, phenylpropanolamine, naltrexone, atomoxetine, vasopressin, modafinil, antioxidants

Cognitive Impairment

May impede recovery

haloperidol
phenothiazines
prazosin
clonidine
phenoxybenzamine
GABAergic agents
benzodiazepines
Phenytoin
Carbamazepine?
Topiramate?
phenobarbital
Idazoxan

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, PTSD)
• Also use behavioral interventions

*Writer & Schillerstrom, J Neuropsychiatry Clin Neurosci 2009*
Aggression, Agitation, Impulsivity
(none FDA approved for this indication)

- **Acute**
  - Antipsychotics (e.g., quetiapine 25-100mg bid)
  - Benzodiazepines (e.g., clonazepam 0.5mg bid)
- **Chronic**
  - Beta-blockers - e.g. propranolol – may need up to 200mg/d in some cases, pindolol, nadolol
  - valproate, carbamazepine, gabapentin, lamotrigine
  - Lithium (neurotoxicity, narrow therapeutic window)
  - buspirone
  - Serotonergic antidepressants (e.g., SSRIs, trazodone)
  - tricyclic antidepressants (e.g., nortriptyline, desipramine)
  - Antipsychotics (esp. second and third generation)
    - amantadine, bromocriptine, bupropion
    - clonidine, methylphenidate, naltrexone, estrogen, dronabinol

Pilot study of sertraline (N=15)
Brief Anger / Aggression Questionnaire (BAAQ)

Hypopituitarism

- Unrelated to TBI severity in most studies
- Growth hormone deficiency, hypogonadism
- Can be assoc. with anxiety, depression, fatigue, irritability, insomnia, sexual dysfunction, cognitive impairment
- Assess GH-IGF-1 axis
- Hormone replacement may help

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 Severity

+/ -

Psychiatric Vulnerability

TBI

Cognition

+/ -

Neuropsychiatric Symptoms

+/ -

Postconcussive Symptoms

Functioning/ QOL

Health Care Utilization

References


