Pharmacotherapy for Behavioral, Emotional, and Cognitive Symptoms in Brain Injury

Presented by: Matthew Peters, MD
October 22, 2025

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Disclosures

- None relevant to this presentation

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Webinar Series Schedule

- **Session 1 (10/9/25):** Introduction and Recognizing Behavioral, Emotional, and Cognitive Symptoms in Brain Injury
- Session 2 (10/23/25): Pharmacotherapy for Behavioral, Emotional, and Cognitive symptoms in Brain Injury
- **Session 3 (11/6/25):** Psychotherapeutic Approaches, Psychosocial Education, and Family Support for Patients with Brain Injury
- **Session 4 (12/4/25):** Structuring Environments for Safe, Therapeutic Management of Brain Injuries and Seminar Series Recap and Wrap-up

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Re-Introductions


Matthew Peters, MD


Durga Roy, MD


Peggy Reisher, MSW

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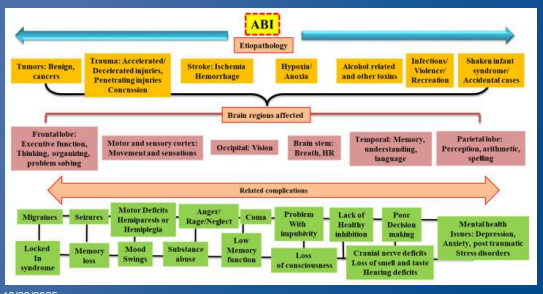
Session 1 Recap – Brain Injury Types



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Session 1 Recap – Cognitive Symptoms

Cognitive Dyscontrol	**Malfunction in planning, decision-making, and learning abilities**
Slower processing speed	Decreased rate in acquiring, processing and responding to new information
Poor verbal learning	Inability to acquire, retain and utilize information through language
Impaired executive function	Impairment in goal-directed behavior involved in organizing thoughts and purposeful tasks

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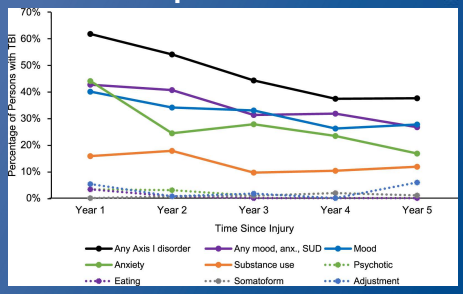
Session 1 Recap – Other NPS



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Session 1 Recap - OBISSS

Online Brain Injury Screening and Support System

Online Brain Injury Screening and Support System
- Helps identify lifetime history of brain injury
- Offers tip sheets to help manage symptoms
- Self-administered
- Free for all to use
- Note: This screening tool is not a medical evaluation and does not provide a diagnosis.

Access OBISSS Now:

OBISSS Link: nashia.org/obisss

State: Nebraska
Password: 402

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Session 2 Objectives

- Describe the general approach to pharmacotherapy for cognitive and other neuropsychiatric symptoms (NPS) following brain injury
- Recognize the most common pharmacologic agents used in this context
- Identify the most common side effects that may occur from these pharmacologic agents

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Real-Time Case Discussions

- Following the break, Drs. Peters & Roy will lead real-time case discussions
- As a participant, we encourage you to present an interesting case or a case you'd like advice or feedback on
- For this session, the case discussion will focus on neuropsychiatric symptom treatment
- Important details when presenting:
  - The case must NOT contain identifying information
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  - Present the most relevant components of the case as they pertain to symptom presentation and patient evaluation – Ideally 5 minutes or less
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NPS Treatment Approach

- Multidisciplinary care is essential, but not always available
  - Physical Medicine & Rehabilitation
  - Neuropsychiatry / Behavioral Neurology
  - Neuropsychology
  - Occupational Therapy
  - Physical Therapy
  - Speech Language Pathology

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NPS Treatment Approach

- Both neuropsychiatric and idiopathic psychiatric conditions can occur / co-occur
- Brain injury may change the nature of a previously well-treated mental health condition

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NPS Treatment Approach

- Multi-modality care is often required
  - **Pharmacotherapy**
  - Psychotherapy
  - Cognitive rehabilitation
  - Family therapy
  - Vocational rehabilitation
- Pharmacotherapy is often NOT the most important!

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NPS Pharmacotherapy

- No FDA-approved medications for NPS following brain injury
- Limited and fragmented evidence
- Often treating symptoms rather than syndromes
- Start low, go slow, don't stop

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Post-concussive Syndrome (PCS)

- Fatigue, sleep disturbance, headache, dizziness, irritability, affective dysregulation, apathy, personality changes
  - Greatest within first week
  - Most cases resolve by one month
  - 10-15% may last one year or longer
- Important to assess for spontaneous resolution
- Hard to know where to draw the line for PCS vs. long-term NPS
- For PCS, simple reassurance is usually the best treatment

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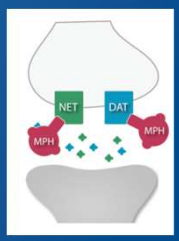
Treatment of Cognitive Symptoms

- **Methylphenidate: m**ultiple studies support its use to improve processing speed and attention
  - Increases the levels of dopamine and norepinephrine by blocking reuptake
  - Enhances attention, focus, motivation, and reduces impulsivity
  - SIDE EFFECTS: insomnia, decreased appetite, dysphoria, irritability, tics, headache, blurred vision



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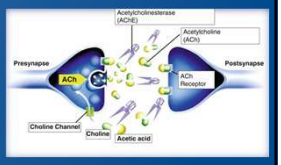
Treatment of Cognitive Symptoms

- **Donepezil:** small effect sizes, but found to improve memory and attention
  - Increases availability of acetylcholine by blocking the acetylcholinesterase enzyme
  - Improves memory, thinking, communication skills
  - SIDE EFFECTS: diarrhea, nausea, headache, dizziness, drowsiness; can cause bradycardia and syncope



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Treatment of Cognitive Symptoms

- **Amantadine:** smaller studies have shown improved executive functioning and cognitive recovery, but not seen in larger trials
  - Mechanism not fully understand, but appears to increase dopamine release, stimulate norepinephrine response, and has NMDA receptor antagonism
  - Improved functioning; may hasten cognitive recovery in intermediate term
  - SIDE EFFECTS: nausea, dizziness, insomnia, constipation

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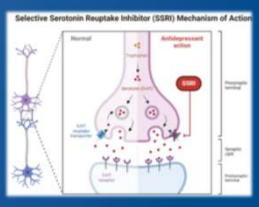
Treatment of Depression

- **Can be more difficult to treat post-brain injury**
- **Sertraline & Citalopram: have the most evidence**
  - Both are selective serotonin reuptake inhibitors (SSRIs) that block the reuptake of serotonin
  - Improved depression and associated symptoms
  - SIDE EFFECTS: nausea, diarrhea, insomnia, sexual dysfunction, weight gain



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Treatment of Depression

- **Methylphenidate: trial comparing placebo, sertraline, and methylphenidate supported its use for depression + added benefits**
  - Increases the levels of dopamine and norepinephrine by blocking reuptake
  - In the above trial, depressive symptom improvement was comparable to sertraline and had added benefit of improved cognition and alertness
  - Makes it an interesting choice for apathy syndromes!
  - SIDE EFFECTS: insomnia, decreased appetite, dysphoria, irritability, tics, headache, blurred vision

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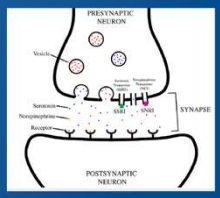
Treatment of Anxiety

- **In addition to SSRIs, one retrospective study showed utility of venlafaxine**
  - Venlafaxine is a selective norepinephrine reuptake inhibitor (SNRI) that blocks the reuptake of norepinephrine
  - Improved anxiety and associated symptoms
  - SIDE EFFECTS: nausea, sweating, headaches, dizziness, insomnia; can have a withdrawal syndrome



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Treatment of Anxiety

Benzodiazepines are not recommended and can cause paradoxical agitation in some patients

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Treatment of PTSD

- **Risk still exists even if don't remember the event**
- **SSRIs are the most common with sertraline having with best evidence**
  - Sertraline, fluoxetine, and paroxetine are FDA-approved for treatment of PTSD
  - Reduced intensity of intrusive memories, hyperarousal, negative emotions
  - SIDE EFFECTS: nausea, diarrhea, insomnia, sexual dysfunction, weight gain

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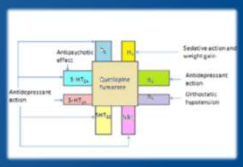
Treatment of Mania

- **Mania with psychosis most common variant**
- **In acute phase, atypical antipsychotics used with most common being quetiapine**
  - Blocks dopamine D2 receptors and rapidly dissociates; blocks serotonin 5-HT2A receptors
  - Stabilize mood and reduce impulsive behaviors
  - SIDE EFFECTS: sleepiness, weight gain, dizziness, dry mouth, headache, increase appetite



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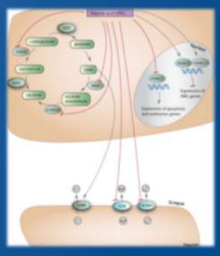
Treatment of Mania

- **Mania with psychosis most common variant**
- **In maintenance phase, mood stabilizers with most common being depakote**
  - Complicated mechanism of action: increasing GABA and blocking voltage-gated ion channels
  - Stabilize mood and reduce impulsive behaviors
  - SIDE EFFECTS: nausea, diarrhea, sleepiness, weight gain, hair thinning, coordination problems



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Treatment of Psychosis

- **Evidence base limited and concern exists for delayed neuronal recovery from dopamine antagonism**
- **Evidence exists for quetiapine, olanzapine, and risperidone**
  - Block dopamine D2 receptors and serotonin 5-HT2A receptors
  - Improvement in hallucinations, delusions, thought disorder, irritability
  - SIDE EFFECTS: sleepiness, weight gain, dizziness, dry mouth, headache, increase appetite; extra-pyramidal symptoms an issue with higher doses of risperidone

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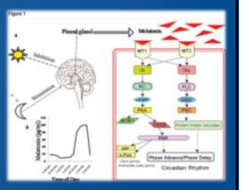
Treatment of Insomnia

- **Non-pharmacologic options are essential**
- **Melatonin 2mg showed benefit in one study but 5mg showed no benefit in another**
  - Supplements the body's natural supply of melatonin
  - Enhances the drive for sleep and shifts the circadian clock
  - SIDE EFFECTS: daytime drowsiness, headache, dizziness, vivid dreams



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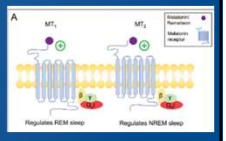
Treatment of Insomnia

- **Small studies suggest trazodone may be beneficial**
- **A placebo-controlled trial showed the potential utility of ramelteon**
  - Melatonin receptor agonist
  - Enhances the drive for sleep and shifts the circadian clock
  - SIDE EFFECTS: daytime drowsiness, headache, dizziness, worsening of insomnia



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Treatment of Behavioral Disturbances

- Agitation is one of the most debilitating symptoms following TBI
- Nonpharmacologic approaches are highly emphasized
- A key goal is to avoid deliriogenic medications
  - e.g., benzodiazepines, haloperidol

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Treatment of Behavioral Disturbances

- Atypical antipsychotics (e.g., quetiapine, olanzapine)
- Some evidence for valproic acid
- Mixed evidence for methylphenidate
- Amantadine has mixed evidence for improving irritability and agitation
- Antidepressants and beta-blockers may serve a role
- ECT has been used in cases as a last resort

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Treatment of Behavioral Disturbances

CPG Recommendations	SIGN	INESSS-ONF
Assessment		
Comprehensive, individualised neurobehavioural assessment		Level C Recommendation
Clinicians should carefully define and characterise neurobehavioural issues through diagnostic interviews and direct observations		Level C Recommendation
Assess for differential causes of agitation prior to treatment	Good Practice Point	
Non-Pharmacological	Not Reported	
Behaviour management plan considering precipitating factors, triggers or antecedents possibly contributing to behaviour and reinforcing events		Level B Recommendation
A person with TBI with significant challenging behaviours may require a combination of both non-pharmacological and pharmacological approaches for optimal treatment. Ideally, a sequenced approached should be used to determine effective components		Level C Recommendation

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Treatment of Behavioral Disturbances

Pharmacological		
Severe acute agitation that threatens staff or patient safety:		
Neuroleptic medications or intramuscular benzodiazepine		Level C Recommendation
Severe agitation and aggression that threatens staff or patient safety:		
Second generation atypical oral neuroleptic medication		Level C Recommendation
Moderate agitation and irritability:		
Selective serotonin reuptake inhibitors (SSRI) (sertraline considered as first SSRI option)		Level B Recommendation
Tricyclic antidepressants (nortriptyline or desipramine are preferable)		Level C Recommendation
Aggression:		
Beta-blockers (propranolol or pindolol preferable)	Grade B Recommendation	Level A Recommendation
Anti-epileptics (valproate preferable particularly for those with concomitant seizure disorder)		Level C Recommendation
Impaired arousal or attention in agitation:		
Adamantanes (Amantadine) or CNS stimulants (methylphenidate)		Level B Recommendation

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Conclusion

- Multi-specialty and multi-modality care is often necessary, and pharmacotherapy is often NOT the most important
- There are no FDA-approved medications for treatment of NPS following brain injury
- Start low, go slow, don't stop
- Don't forget about post-concussive syndrome, which can self-resolve
- Although the evidence base is limited, there is some guidance on what medications to try first for treatment of NPS following brain injury

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Thank You!

- Questions?

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