Pharmacologic Treatment of Neurobehavioral Effects of Traumatic Brain Injury

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The presenter has no actual or potential conflict of interest in relation to this program.
Craig Hospital

- Specialty rehabilitation of TBI and SCI patients
- Ranked in the Top 10 rehabilitation hospitals by *U.S. News & World Report* for over 20 years
- Federally designated as a Model Systems Center for both TBI and SCI research
- TBI National Statistical Database
TBI Model Systems

- Funded by National Institute on Disability and Rehabilitation Research (NIDRR)
- Partner with VA, DOD, and NIH
- Currently 16 TBIMS centers
- Systematically collect data for research analysis
- Stimulate more rigorous research
Objectives

- Describe obstacles for developing standards of care for pharmacologic treatment of brain injury effects.
- Identify medications used to treat effects after traumatic brain injury and recognize possible side effects from these medications.
- List some medications that should be used with caution in patients recovering from brain injury.
Guidelines for the Pharmacologic Treatment of Neurobehavioral Sequelae of Traumatic Brain Injury

### Evidence Based Practice

<table>
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<tr>
<th>Standards</th>
<th>Guidelines</th>
<th>Options</th>
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<tbody>
<tr>
<td>Based on at least 1, well-designed class I study with adequate sample OR overwhelming class II evidence</td>
<td>Based on well-designed class II studies</td>
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Obstacles to Developing Standards of Care

- Heterogeneity of patient population
  - Individual injury
    - Neuroanatomy
    - Neurophysiology
    - Neurochemistry
  - Variability of brain function
    - Pre–morbid brain function
    - Post–traumatic sequelae
Obstacles to Developing Standard of Care

- Variable responses to medications
  - Some patients benefit
  - Some patients get worse
  - Some patients more sensitive
  - Some patients resistant or need extreme doses

- Compliance issues
  - Memory
  - Adverse effects and interactions
Obstacles to Developing Standards of Care

- Measuring cognition and behavior
  - Patient may test well, but function poorly
  - Patient may test poorly, but function well

- Variations in biochemistry balance
  - Serotonin
  - Dopamine
  - Acetylcholine
  - Norepinephrine

* Lack of evidence ≠ lack of efficacy *
**Neurotransmitters**

- **Serotonin**
  - Memory
  - Emotion
  - Sleep/wake

- **Dopamine**
  - Voluntary movement
  - Motivation

- **Acetylcholine**
  - Memory
  - Parasympathetic nervous system

- **Norepinephrine**
  - Wakefulness
  - Arousal
Neurotransmitters

- Glutamate
  - NMDA receptor
  - Cognition
  - Overstimulation → cell death

- GABA
  - Inhibitory neurotransmitter
Treatment Plan

Injury → Correlating neurotransmitter(s) → Symptom(s)

- Acute
- Subacute
- Chronic

Changes by phase

• Start low, go slow
• One intervention at a time

Re-evaluate
Brain Injury Sequelae

- **Cognitive deficiencies**
  - Attention/concentration and speed of processing
  - Memory
  - Executive functions
- **Behavioral**
- **Emotional**
- **Other**
  - Fatigue
  - Insomnia
  - Aphasia
  - Pseudobulbar affect (PBA)
Treatment of Cognitive Deficiencies

- Dopamine, acetylcholine, serotonin, norepinephrine
- No “standards”, just guidelines and options
- Dopamine enhancers
  - Bromocriptine (Parlodel®)
    - Guideline-level recommendation
    - Executive functioning
      - Divided attention
      - Initiation
      - Mental flexibility
Treatment of Cognitive Deficiencies

- Dopamine enhancers
  - Amantadine (Symmetrel®)
    - NMDA antagonist
    - General cognitive functions
    - Attention/concentration and speed of processing
    - Apathy/poor initiation
    - Motivation
    - Perseveration
Treatment of Cognitive Deficiencies

- Dopamine enhancers
  - Carbidopa/levodopa (Sinemet®), pramipexole (Mirapex®), selegiline (Eldepryl®)
    - Initiation
    - Alertness
    - Wakefulness
Treatment of Cognitive Deficiencies

- **Stimulants**
  - Methylphenidate (Ritalin®)
    - Dopamine and norepinephrine
    - Guideline- and option-level recommendations
    - Memory
    - Attention/concentration and speed of processing
    - Mental processing
    - Learning
    - Arousal
    - Apathy/poor initiation
    - General cognitive functions
Treatment of Cognitive Deficiencies

- **Stimulants**
  - Dextroamphetamine (Dexedrine®)
    - Dopamine and norepinephrine
    - Attention
    - Working memory
  - Modafinil (Provigil®)
    - Dopamine, histamine, alpha-1 agonist, inhibits GABA
    - Attention
    - Apathy/poor initiation
    - Memory
    - Speed of processing
Treatment of Cognitive Deficiencies

- Acetylcholinesterase inhibitors
  - Donepezil (Aricept®)
    - Guideline-level recommendation
    - Better general functioning
    - Attention/concentration and speed of processing
    - Learning
    - Memory
    - Apathy/poor initiation
Treatment of Cognitive Deficiencies

- Acetylcholinesterase inhibitors
  - Other acetylcholinesterase inhibitors
    - Galantamine (Razadyne®)
    - Rivastigmine (Exelon®)
    - Physostigmine
Other options

- Memantine (Namenda®)
  - NMDA receptor antagonist
  - Cognitive function
  - Memory

- Bupropion (Wellbutrin®)
  - Dopamine and norepinephrine reuptake inhibitor
  - Cognitive function
Other options

- Atomoxetine (Strattera®)
  - Selective norepinephrine reuptake inhibitor
  - Attention (lower doses)
  - Memory
  - Arousal (higher doses)
  - Apathy/poor initiation
  - Speed of processing
Self-Assessment Question

A 51 y/o female involved in a MVA resulting in diffuse axonal injury is experiencing deficits in wakefulness, arousal, purpose, and initiation. An appropriate neurotransmitter target for pharmacotherapy includes:

- A. Glutamate agonist
- B. GABA agonist
- C. Dopamine agonist
- D. Dopamine antagonist
Treatment of Aggression

- Disruption to dopamine, norepinephrine, acetylcholine, serotonin
- No standards
- Guideline-level recommendations
  - Propranolol (Inderal®)
  - Pindolol
Treatment of Aggression

- Options
  - Antihypertensives
    - Metoprolol (Lopressor®)
    - Clonidine (Catapres®)
  - Mood stabilizers
    - Carbamazepine (Tegretol®)
    - Valproic acid (Depakote®)
    - Lithium (Lithobid®)
Treatment of Aggression

Options

- Antidepressants
  - Sertraline (Zoloft®)
  - Paroxetine (Paxil®)
  - Fluoxetine (Prozac®)
  - Citalopram (Celexa®)

Options

- Antidepressants
  - Trazodone (Desyrel®)
  - Amitriptyline (Elavil®)
  - Desipramine (Norpramin®)
  - Protriptyline (Vivactil®)
Treatment of Aggression

- **Options**
  - **Hormones**
    - Estrogens
    - Medroxyprogesterone (DepoProvera®)
  - **Others**
    - Amantadine (Symmetrel®)
    - Buspirone (Buspar®)

- **Options**
  - **Atypical antipsychotics**
    - Risperidone (Risperdal®)
    - Clozapine (Clozaril®)
    - Olanzapine (Zyprexa®)
    - Quetiapine (Seroquel®)
    - Ziprasidone (Geodon®)
  - **Stimulants**
    - Methylphenidate (Ritalin®)
    - Dextroamphetamine (Dexedrine®)
A patient’s brain CT scan shows bilateral frontal and diffuse axonal injury. He is impulsive and agitated. The best option for pharmacologic treatment of his agitation is:

- A. Haloperidol
- B. Diazepam
- C. Diphenhydramine
- D. Propranolol
Treatment of Psychiatric Disorders

- Serotonin, norepinephrine, dopamine
- Depression/emotional deficits
  - Antidepressants (TCA and selective serotonin reuptake inhibitors)
    - Nortriptyline (Pamelor®)
    - Amitriptyline (Elavil®)
    - Desipramine (Norpramin®)
    - Citalopram (Celexa®)
    - Escitalopram (Lexapro®)
    - Paroxetine (Paxil®)
    - Sertraline (Zoloft®)
Treatment of Psychiatric Disorders

- Depression/emotional deficits
  - Venlafaxine (Effexor®), serotonin/norepinephrine
  - Atomoxetine (Strattera®), norepinephrine
  - Modafinil (Provigil®), ↓ GABA

- Bipolar disorder
  - Valproic acid (Depakote®)
  - Carbamazepine (Tegretol®)
  - Lithium

- Psychosis
  - Olanzapine (Zyprexa®)
  - Clozapine (Clozaril®)
Treatment of Psychiatric Disorders

- Anxiety
  - Tricyclic antidepressants (TCA)
  - Selective serotonin reuptake inhibitors (SSRI)
  - Benzodiazepines
    - Lorazepam (Ativan®)
    - Clonazepam (Klonopin®)
    - May interfere with cognition
An obstacle to treating a TBI patient with depression includes:

- A. The patient may be more sensitive or less responsive to medication
- B. The patient’s previous history does not contribute to current symptoms
- C. Depression in TBI patients is not affected by neurotransmitters
- D. Two medications should be started simultaneously
Medications for Fatigue

- Acetylcholinesterase inhibitors
- Methylphenidate (Ritalin®)
- Modafinil (Provigil®)
- Atomoxetine (Strattera®)
Medications for Insomnia

- Trazodone (Desyrel®)
- Imipramine (Tofranil®)
- Nortriptyline (Pamelor®)
- Mirtazapine (Remeron®)
- Ramelteon (Rozerem®)
Medications for Aphasria

- Tricyclic antidepressants
  - Nortriptyline (Pamelor®)
  - Desipramine (Norpramin®)
- Increase serotonin and norepinephrine
Pseudobulbar Affect (PBA)

- Uncontrollable, inappropriate affect
- Some success
  - Antidepressants (TCA, SSRI)
  - Dopaminergic agents
Pseudobulbar Affect (PBA)

- Dextromethorphan/quinidine (Nuedexta®)
  - Discovered while studying different use for ALS
  - Dextromethorphan
    - Cough suppressant
    - NMDA antagonist
  - Quinidine
    - Antiarrhythmic agent
    - Slow metabolism of dextromethorphan
Side Effects

- Are sometimes “therapeutic”
- Vary among medications in each class
- Guide medication selection
- Make some medications inappropriate for brain injury patients
Medications to Use with Caution in TBI

- Benzodiazepines
  - Exacerbate confusion ("benzodiazepine psychosis")
  - Impairs memory
  - Common for insomnia and agitation
  - Stopping the medication may be the "therapeutic event"
Medications to Use with Caution in TBI

- First generation antipsychotics
  - Block dopamine $\rightarrow$ interferes with recovery
  - Sedation $\rightarrow$ confusion $\rightarrow$ exacerbate aggression
  - Stopping medication can be therapeutic

- Phenytoin (Dilantin®)
  - Anticonvulsant
  - Impairs cognitive function recovery initially
  - Better alternatives for seizure prophylaxis
A TBI patient recently transferred from the ICU has been receiving haloperidol for aggressive behavior. He continues to be assaultive toward caregivers, especially at night. The best intervention would be:

- A. Adding lorazepam PRN
- B. Adding amantadine PRN
- C. Increasing the haloperidol dose
- D. Stopping the haloperidol
A TBI patient with a pre-morbid history of seizure disorder is currently receiving levetiracetam and phenytoin. An intervention to facilitate cognitive recovery would be:

- A. Stop levetiracetam and increase phenytoin dose
- B. Stop phenytoin and add lacosamide
- C. Add phenobarbital
- D. Avoid making any changes to current regimen
Summary

Obstacles to good evidence
- Heterogeneity of patient population
- Variable responses to medications
- Variations in biochemistry balance
- Measuring cognition and behavior
- Compliance issues
Summary

- Limited evidence
  - Few standards
  - Few guidelines
  - Lots of options
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Summary

- Side effects to monitor
  - Sexual side effects
  - Headache, GI
  - Dizziness
  - Insomnia
  - Sedation
  - Weight gain
  - Extrapyramidal symptoms
Summary

- Medications to try to avoid
  - Benzodiazepines
  - First generation antipsychotics
  - Phenytoin (Dilantin®)
Thank you for your attention.
Selected References


