Review of Neuropharmacology in Pediatric Brain Injury
• John Pelegano MD (15 minutes): Introduction, Audience Response System tips, and initial case presentations
• 2. Jilda Vargus-Adams MD,MSc (30 minutes): Neuropharmacologic agents to increase arousal
• 3. Micah Baird MD (30 minutes): Neuropharmacologic agents for agitation and improved cognition.
• 4. Break (10 Minutes)
• 5. John Pelegano MD (15 minutes): The unusual story of zolpidem, conclusion of case presentations.
• 6. Jilda Vargus-Adams MD,MSc (20 minutes): Clinical experiences from the audience, Questions & Answers.
Disclosure Information
AACPD 68th Annual Meeting September 10-14, 2014

Speaker Name: Jilda Vargus-Adams MD MSc

Disclosure of Relevant Financial Relationships
I have the following financial relationships to disclose:
Grant/Research support from: Cerebral Palsy International Research Foundation, Merz

Disclosure of Off-Label and/or investigative uses:
I will discuss the following off label use and/or investigational use in my presentation:
Virtually every medication discussed in this presentation including amantadine, carbidopa/levodopa, bromocriptine, methylphenidate, and zolpidem
Neuropharmacology for Arousal in Brain Injury

• Disorders of Consciousness
  – Descriptions
  – Assessments

• Treatment of Disorders of Consciousness
  – Environmental and general medical management
  – Neuropharmacology with Dopaminergic agents
Severe Disorders of Consciousness

• Severely altered arousal and/or awareness of self and the environment
  – Coma
  – Vegetative State
  – Minimally Conscious State

Consensus definitions from Aspen Neurobehavioral Workgroup
Anatomic structures subserving awareness and arousal

Bfb: Basal forebrain
Hypo: Hypothalamus
Thal: Thalamus
ARAS: Ascending reticular activating system

Weiss et al., Critical Care, 2007
Coma  (ALL criteria must be met)

- No spontaneous or induced eye opening**
- No command following
- No intelligible speech
- No purposeful movement
- No discrete defensive capacity to localize noxious stimuli
- Rarely lasts longer than 2-4 weeks after trauma; evolves to vegetative state

**Bilateral ptosis can also occur in setting of cranial nerve injuries**
Vegetative State (ALL criteria must be met)

- Presence of sleep-wake cycles (periodic eye opening)
- No sustained, reproducible, purposeful, or voluntary behavioral responses to stimuli
- No evidence of language comprehension
- Bowel and bladder incontinence
- Preservation of autonomic functions permits survival with adequate care
- Variable preservation of cranial/spinal reflexes
Brand new terminology

Vegetative State =>

“Unresponsive Wakefulness Syndrome”
Behaviors Consistent with Vegetative State**

- Spontaneous movement
- Startle myoclonus
- Smile
- Shed tears
- Moan, grunt, scream

** When inconsistent, nonpurposeful, coordinated only reflexively
Prolonged Vegetative States

• Current recommendation:
  – Describe as:
    • Vegetative State +
    • Etiology +
    • Duration
  – Eliminate use of
    • “Persistent Vegetative State”
    • “Permanent Vegetative State”
“Late Awakenings”  (never say never)

• Donald Hebert – firefighter “wakes up” and converses with family 10 years after anoxic BI (attributed to medication cocktail)

• Terry Wallis – “wakes up” and talks, then regains motor function, 19 years after TBI (attributed to axonal regrowth)
Minimally Conscious State

• Behaviors are **inconsistent** but reproducible or sustained enough to differentiate from reflex

• Clearly discernable evidence of **any one** of:
  
  – Simple command following
  
  – Gestured or verbal yes/no response
  
  – Intelligible verbalization
  
  – Movements or affective behaviors that occur in contingent relation to relevant stimuli and are not reflexive activity
Minimally Conscious State: contingent behavioral responses

- Pursuit eye movement or sustained fixation in direct response to moving or salient stimuli
- Crying, smiling, or laughing in response to emotional but not neutral content
- Vocalization or gestures in direct response to linguistic content of comments or questions
- Reaching for objects with a clear relationship between object location and direction of reach
- Touching or holding objects in a manner that accommodates the size and shape of the object
More brand new terminology

MCS (-)
- Minimal levels of behavioral interaction characterized by the presence of non-reflex movements such as: (i) orientation of noxious stimuli, (ii) pursuit eye movements that occur appropriately in relation to relevant environmental stimuli.

MCS (+)
- Presence of (i) command following, (ii) intelligible verbalization or (iii) gestural or verbal yes/no responses.
Emergence from MCS

• Return of reliable and consistent interactive communication OR functional object use
  – Communication may be through verbalization, writing, yes/no signals, or augmentative communication device (6/6 correct responses to situational orientation questions)
  – Functional object use: discrimination and appropriate use of at least 2 common articles (cup, hairbrush, etc)
Recommendations for Assessment

• Optimize patient’s arousal/attention
  – Minimize sedating medications
  – Provide sufficient stimulation
  – Choose a distraction-free environment

• Choose target behavior carefully
  – Family/therapist input
  – Consider impairments
  – Non-reflexive movements
  – Use broad range of stimuli/responses

• Serially re-assess
Standardized Evaluation Tools

• Evaluate responses to many different stimuli
• May require training to administer

JFK Coma Recovery Scale – Revised (CRS-R)
Rappaport Coma/Near Coma Scale (CNCS)
Western Neuro Sensory Stimulation Profile (WNSSP)
JFK Coma Recovery Scale - Revised

- Auditory Function
- Visual Function
- Motor Function
  - Functional object use*
- Oromotor/Verbal Function
- Communication
  - Functional communication*
- Arousal
Rappaport Coma/Near Coma Scale

- Command Following
- Vocalization
- Motor responses to
  - Pain
  - Visual stimulation/threat
  - Tactile stimulation
  - Olfactory stimulation
  - Auditory stimulation
Contrast of Standardized Scales

JFK Coma Recovery Scale (Revised)

• Motor Function
  – Noxious Stimulation:
    • 1: No response
    • 2: Abnormal posturing
    • 3: Flexion withdrawal
    • 4: Localization
  – Object Interaction
    • 5: Manipulation
    • 6: Automatic Motor Response
    • 7: Functional Use

Rappaport Coma/Near-Coma Scale

• Motor Response
  – Command Following
  – Shoulder tap
  – Nasal swab
  – Nail bed pressure
  – Ear pinch/pull
Environmental Interventions to Optimize Responsiveness

• Optimize stimulation
  – Position upright – wheelchair or stander
    • Even better – get the child out of the wheelchair
  – Lights on during day
  – Multi-sensory stimulation, including movement
  – ...but not too much stimulation

• Optimize sleep
  – Nighttime routine
  – Lights off/noises off at night
  – May need daytime naps/rest breaks
A structured medical approach to optimize responsiveness

• Wean potentially sedating medications

• Optimize night-time sleep
  – Trazodone
  – Melatonin

• Evaluate and optimize hearing and vision

• Await stabilization of active medical issues (?)

• Consider neurostimulant trial(s)
Minimizing Sedating Medications

**Sedating Medications**

- Tone meds:
  - Baclofen
  - Tizanidine
  - Benzodiazepines

- GI meds
  - H2-blockers
  - Metoclopramide

- Narcotics

- Cardiovascular agents
  - Clonidine
  - Propranolol

**Less Sedating Alternatives**

- Tone meds:
  - Dantrolene (? Sedating)
  - Carbidopa/Levodopa
  - Botulinum toxin

- GI meds
  - PPI
  - Erythromycin

- Other pain meds

- Cardiovascular agents
  - Alternate anti-hypertensives
  - Alternate beta-blockers
Dopaminergic Agents

• Dopamine deficiency often follows TBI

• Multiple agents available, with varying levels of evidence
  – Amantadine
  – Carbidopa/Levodopa
  – Bromocriptine
  – Pramipexole
  – Methylphenidate
Amantadine

- Pre-synaptic and post-synaptic dopamine agonist
- Used in all states of consciousness following TBI (facilitation of arousal from coma through optimization of attention, processing speed for higher-level cognitive tasks)
- Variability in published reports re: efficacy
- Initially developed as anti-viral agent, also used in Parkinson’s disease
Amantadine:
RCT in adults with VS or MCS after TBI

Giacino et al., NEJM, 2012
Double-blind placebo-controlled cross-over study of amantadine in children with acquired brain injury

**TABLE 1** Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, yrs</th>
<th>Sex</th>
<th>Mechanism of Injury</th>
<th>Initial GCS</th>
<th>Weeks When Postinjury Enrolled</th>
<th>Maximum Dose, Milligram Twice a Day</th>
<th>Level of Consciousness</th>
<th>End First Arm</th>
<th>W</th>
<th>End Second Arm</th>
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<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>M</td>
<td>Anoxia</td>
<td>3</td>
<td>9</td>
<td>120</td>
<td>VS</td>
<td>VS</td>
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<td>VS</td>
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<tr>
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<td>VS</td>
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<tr>
<td>4</td>
<td>13</td>
<td>M</td>
<td>Trauma</td>
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<td>6</td>
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<td>VS</td>
<td>VS</td>
<td>VS</td>
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<tr>
<td>5</td>
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<td>M</td>
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<td>6</td>
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<td>VS</td>
<td>VS</td>
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<tr>
<td>6</td>
<td>16</td>
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<td>3</td>
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<td>MCS</td>
<td>VS</td>
<td>MCS</td>
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<td>7</td>
<td>14</td>
<td>F</td>
<td>Stroke</td>
<td>4</td>
<td>6</td>
<td>165</td>
<td>MCS</td>
<td>MCS</td>
<td>MCS</td>
<td>CS</td>
</tr>
</tbody>
</table>

* Denotes amantadine arm.

* Denotes subjects not included in analysis.

W, washout; VS, vegetative state; MCS, minimally conscious state; CS, fully conscious state; GCS, Glasgow Coma Scale.

Pramipexole

- Non-ergoline Dopamine agonist
- Not much published...
- Approved for use in early Parkinson’s disease and restless leg syndrome
Double-blind study of Amantadine vs Pramipexole in children with severe TBI (n=10)

Table 4. Comparison of Rates of Change (Slope) on Medication (Either Pramipexole or Amantadine) in the Premedication, Medication, and Postmedication Phases for Each of the Outcome Measures

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Trial Phase</th>
<th>Rate of Change</th>
<th>Pairwise Comparison P Value*</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td>Coma Near Coma Scale</td>
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<tr>
<td></td>
<td>Premedication</td>
<td>−0.80</td>
<td>3.68</td>
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<tr>
<td></td>
<td>Medication</td>
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<td>Postmedication</td>
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<td>0</td>
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<td>Western NeuroSensory Stimulation Profile</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Premedication</td>
<td>0</td>
<td>1.83</td>
</tr>
<tr>
<td></td>
<td>Medication</td>
<td>5.61</td>
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<tr>
<td></td>
<td>Postmedication</td>
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<td>2.37</td>
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<tr>
<td>Disability Rating Scale</td>
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<tr>
<td></td>
<td>Premedication</td>
<td>−0.20</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>Medication</td>
<td>−1.08</td>
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<tr>
<td></td>
<td>Postmedication</td>
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<td>0.47</td>
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</table>

*Uses Scheffé’s method for multiple comparisons to compare the medication phase ranks with those from each of the two nonmedication phases. Comparisons of the pre- and postmedication phases were not significant for all three measures (P values not reported).
Carbidopa/Levodopa

• Dopamine precursor classically used in Parkinson’s disease, also used in pediatric movement disorders

• Case study/anecdotal reports of improvements in function for individuals in VS or MCS

• Often considered for use in patients with DOC when there is a co-existing movement disorder
Bromocriptine

- Dopamine agonist – directly binds to dopamine receptors
- Possible efficacy for aphasia after stroke
- Used in autonomic dysregulation ("storming") after TBI
- Used in malignant hyperthermia
- Also used in Parkinson’s disease
Methylphenidate

- Increases extracellular dopamine and norepinephrine
- Typically used for attention, processing speed
- Some evidence that rate, but not overall level, of recovery enhanced in moderate TBI
  - (Plenger et al., Archives of PM&R, 1996)
- One report of shorter ICU and hospital stay after adult severe TBI when started on hospital day #2
  - (Moein et al., Clinical Neurology & Neurosurgery, 2006)
Zolpidem

- Case reports of emergence from chronic VS or MCS in individuals with traumatic or anoxic BI
- Not effective in all individuals
  (1 in 15-20 in adult reports)
- Effect typically lasts hours
- Thought to inhibit pathologic tonic outflow to thalamocortical system, thereby resulting in activation
Tracking Responsiveness in Relationship to Medication Changes

Rappaport CNCS Score

<table>
<thead>
<tr>
<th>Date</th>
<th>Medication Changes</th>
<th>Score</th>
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<tbody>
<tr>
<td>12/09</td>
<td>baseline</td>
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<tr>
<td>12/10</td>
<td>pre-zolpidem</td>
<td>2.76</td>
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<td>12/10</td>
<td>post-zolpidem</td>
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</tr>
<tr>
<td>12/14</td>
<td>carbidopa/levodopa 1/4 tablet</td>
<td>2.76</td>
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<tr>
<td>12/16</td>
<td>carbidopa/levodopa 1/2 tablet</td>
<td>2.18</td>
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<tr>
<td>12/18</td>
<td>carbidopa/levodopa 1 tablet</td>
<td>2.36</td>
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<tr>
<td>12/21</td>
<td>off carbidopa/levodopa</td>
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<tr>
<td>12/23</td>
<td>5mg methylphenidate</td>
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<tr>
<td>12/28</td>
<td>(7.5 mg methylphenidate)</td>
<td>1.81</td>
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<td>(10 mg methylphenidate)</td>
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Suggested References


