A New Understanding of Disorders of Consciousness

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Beth S. Slomine, Ph.D. ABPP
Director of Training and Neuropsychological Rehabilitation Services
Kennedy Krieger Institute
Associate Professor
Johns Hopkins University School of Medicine

Megan E. Kramer, Ph.D.
Postdoctoral Fellow in Neuropsychology
Kennedy Krieger Institute
Johns Hopkins University School of Medicine
Overview of Presentation

• Terminology

• Neurobiology

• Assessment
  • Behavioral assessment tools
  • Neuroimaging

• Interventions
  • Behavioral interventions
  • Neurostimulant medications
  • Deep brain stimulation

• Predicting outcomes
Terminology
Disorders of Consciousness (DOC)

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

- Consensus definitions from Aspen Neurobehavioral Workgroup
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
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
An individual in a vegetative state may:

- Show spontaneous movement
- Smile
- Shed tears
- Moan, grunt, scream

**BUT,** these behaviors are inconsistent, nonpurposeful, and are only coordinated reflexively

New nomenclature: “Vegetative state + etiology + duration”
No longer use “persistent” or “permanent”
Minimally Conscious State (MCS)

- 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
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 (e.g., cup, hairbrush)
NOT Disorders of Consciousness

- **Brain Death:**
  - Absence of clinical brain function (including brainstem)

- **Locked-In Syndrome**
  - Full consciousness, loss of all motor control except for vertical eye movements and blinking
  - Results from injury to ventral pontine regions
Neurobiology
Anatomic structures subserving awareness and arousal

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

Weiss et al., Critical Care, 2007
Cerebral Cortex

Kinney and Samuels, J Neuropath and Exp Neuro, 1994
Etiology of Disorders of Consciousness

- Congenital -- developmental processes

- Acquired
  - Degenerative/metabolic neurological diseases

- Injury
  - Transient, marking a stage in recovery
  - Permanent due to failure to recover from injury
Neuropathology of Vegetative State

Diffuse Cortical Injury

Diffuse Subcortical +/- Brainstem Injury

Thalamic Injury

figure from Kinney and Samuels, J Neuropath and Exp Neuro 1994
Reduced anatomic connectivity in DOC
Reduced functional connectivity in DOC

Boly et al, Human Brain Mapping, 2009
Assessment
Why Assess Responsiveness?

- Help team members (medical, therapy, & educational staff) and families understand current level of function

- Provide information for payors – supporting level of care, equipment needs

- Standardize patients by functional ability for research and clinical purposes

- Evaluate response to interventions

- Aid in prognosis and prediction of further recovery
Methods of Assessment

- Standardized clinical evaluation scales
- Individualized quantitative behavioral assessments
- Neuroimaging
Standardized Evaluation Tools

- Review of 37 articles and 13 scales

- Best measure was Coma Recovery Scale – Revised (CRS-R)
  - Good content validity, internal consistency, interrater reliability

- Several scales recommended with moderate reservations

- Coma-Near Coma Scale (CNC) may be used with major reservations

- Several other scales not recommended

Seel et al., Arch Phys Med Rehab, 2010
Standardized Evaluation Tools

JFK Coma Recovery Scale (Revised)

- Auditory Function
- Visual Function
- Motor Function
  - Functional object use*
- Oromotor/Verbal
- 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
Individualized Assessments

- Target a few behaviors of particular interest
  - Short assessments
  - Can be repeated throughout day by varying staff and family members

- Examples:
  - Arousal: eye opening, response to stimulus
  - Command following versus automatic movements
  - Vision/Hearing: preferential attention to salient stimuli
Recommendations for Assessment

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

- Optimize patient’s arousal/attention
  - Minimize sedating medications
  - Provide sufficient stimulation
  - Choose a distraction-free environment
## Command Following Protocol

<table>
<thead>
<tr>
<th></th>
<th>Opens Mouth</th>
<th>Sticks Out Tongue</th>
<th>No Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stick out your tongue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(No Command)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open your mouth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stick out your tongue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open your mouth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(No command)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(No command)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open your mouth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stick out your tongue</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Command Following Protocol

Percent of trials with targeted behavior
Imaging as evaluation tool?

Owen et al., Science, 2006
Neuroimaging – a larger cohort

- 5 of 54 patients in VS or MCS demonstrated “willful modulation of brain behavior”

- One patient with in MCS (but no functional communication) correctly answered 5 of 6 yes/no questions by imagining tennis versus spatial navigation

Monti et al., NEJM, 2010
Imaging: network approach

- Observational fMRI study
- Object naming task
- Patients:
  - MCS=5, VS=3, emerged from MCS=1, LIS=1
- Extent of preservation of language network was correlated with Coma Recovery Scale Score

Rodriguez Moreno et al., Neurology, 2010
Interventions to Optimize Responsiveness
Environmental Interventions

- Optimize stimulation
  - Position upright – wheelchair or stander
  - Lights on during day
  - Multi-sensory stimulation
  - But not too much stimulation

- Optimize sleep
  - Nighttime routine
  - Lights off/noises off at night
  - May need daytime naps/rest breaks
Behavioral Interventions

- Positive reinforcement for desired responses
  - Formal preference assessment often helpful for identifying preferred stimuli

- Shaping purposeful responses for functional use

- Switches
A Structured Medical Approach

- 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)
## Tracking Sleep

| TIME | 600 | 700 | 800 | 900 | 1000 | 1100 | 1200 | 1300 | 1400 | 1500 | 1600 | 1700 | 1800 | 1900 | 2000 | 2100 | 2200 | 2300 | 2400 | 0100 | 0200 | 0300 | 0400 | 0500 |
|------|-----|-----|-----|-----|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
|      | A   | S   | S   | S   | S    | A    | A    | A    | A    | A    | S    | A    | A    | A    | A    | A    | A    | A    | A    | S    | A    | A    | S    | A    | S    | S    |
|      | S   | S   | S   | S   | S    | A    | A    | A    | A    | A    | S    | A    | A    | A    | A    | A    | A    | A    | A    | S    | A    | A    | S    | A    | S    | S    |
|      | S   | S   | S   | S   | S    | A    | A    | A    | A    | A    | S    | A    | A    | A    | A    | A    | A    | A    | A    | S    | A    | A    | S    | A    | S    | S    |
|      | S   | S   | S   | S   | S    | A    | A    | A    | A    | A    | S    | A    | A    | A    | A    | A    | A    | A    | A    | S    | A    | A    | S    | A    | S    | S    |
|      | S   | S   | S   | S   | S    | A    | A    | A    | A    | A    | S    | A    | A    | A    | A    | A    | A    | A    | A    | S    | A    | A    | S    | A    | S    | S    |
|      | S   | S   | S   | S   | S    | A    | A    | A    | A    | A    | S    | A    | A    | A    | A    | A    | A    | A    | A    | S    | A    | A    | S    | A    | S    | S    |
Pharmacological Interventions

- Emerging literature

- Typical agents:
  - Dopaminergic agents
  - Gabaergic agents

- Most studies are open-label, observational, and case studies

- Randomized controlled trials of amantadine
  - Adults
  - Children
ORIGINAL ARTICLE

Pharmacological and electrical stimulation in chronic disorders of consciousness: New insights and future directions

LAIS OLIVEIRA¹,² & FELIPE FREGNI¹,²

¹Laboratory of Neuromodulation, Physical Medicine and Rehabilitation Department, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA and ²Berson-Allen Center for Noninvasive Brain Stimulation, Neurology Department, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

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Abstract
Background: Chronic disorders of consciousness are costly and challenging conditions to treat. Although recent studies that have tested pharmacological and electrical stimulation for these conditions are promising, the optimal intervention, mechanisms of action and side effects of these experimental therapies are unclear.
Objective: To systematically review the clinical results of treatments for vegetative state (VS) and minimally conscious state (MCS) from the last 10 years.
Methods: MEDLINE, LILACS and SCOPUS were searched as data sources. Because the potential bias when search is limited to databases of peer-reviewed journals, reference lists were examined and experts in the field were contacted for other relevant or unpublished articles (i.e. negative studies). No negative unpublished studies were found. Studies were included related to therapeutic interventions in adult MCS or VS patients at least 3 and 12 months after non-traumatic and traumatic injuries, respectively. Eight studies met the inclusion criteria. The following interventions were reviewed: levodopa, amantadine, zolpidem, baclofen, dorsal column stimulation and deep brain stimulation.
Conclusions: The adverse effects that were associated with these treatments were typically mild. Most of the studies demonstrated considerable improvements with the interventions, but their low strength of evidence limit the generalizability of the findings.

Keywords: Vegetative state, minimally conscious state, anoxia, traumatic brain injury, therapy, outcome
Amantadine:
RCT in adults with VS or MCS after TBI

- Recently concluded study
- Double-blind placebo controlled
- Amantadine administered for 4 weeks after admission to acute rehabilitation
- Improved rate of change in DRS during treatment period in amantadine group
- No between-group differences after two week washout period
- No significant adverse effects

Whyte et al., presented at AAPMR 2010
Amantadine: A Pediatric Trial

<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>
</tr>
</thead>
<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>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>M</td>
<td>Trauma</td>
<td>4</td>
<td>4</td>
<td>83</td>
<td>MCS</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>M</td>
<td>Trauma</td>
<td>4</td>
<td>10</td>
<td>99</td>
<td>VS</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>M</td>
<td>Trauma</td>
<td>4</td>
<td>6</td>
<td>72</td>
<td>VS</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>M</td>
<td>Trauma</td>
<td>6</td>
<td>5</td>
<td>149</td>
<td>VS</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>M</td>
<td>Trauma</td>
<td>3</td>
<td>7</td>
<td>175</td>
<td>VS</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>F</td>
<td>Stroke</td>
<td>4</td>
<td>6</td>
<td>165</td>
<td>MCS</td>
</tr>
</tbody>
</table>

*a Denotes amantadine arm.

*b Denotes subjects not included in analysis.

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

McMahon et al., AJPMR, 2009
Vargus-Adams, et al., PM&R, 2010
Zolpidem (Ambien)

- Case reports of emergence from chronic VS or MCS in individuals with traumatic or anoxic BI
- Not effective in all individuals
  - (1 in 15, Whyte, AJPMR, 2009)
- Effect typically lasts hours
- Thought to inhibit pathologic tonic outflow to thalamocortical system, thereby resulting in activation
- Limited data in children

Brefel-Courbon et al., Ann Neurol, 2007
Methylphenidate (Ritalin)

- 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)
Tracking Responsiveness by Medication

Pennington et al., Poster presented at 2011 INS Conference
Deep Thalamic Stimulation

- Stimulation of thalamus proposed to take the role of arousal regulation normally controlled by frontal lobe

- In MCS, improves regulation of functionally connected but inconsistently active brain networks

- Goal is restoration of reliable communication or response initiation/persistence

Schiff et al., Nature, 2007
Predicting Outcomes
Predicting Outcome

- Prognosis is better for MCS vs VS at admission to rehab, and for TBI versus non-TBI (Giacino & Kalmar, 1997; Katz et al., 2009)
Predicting Outcome

- Minimal signs of consciousness at one month post-injury was associated with emergence from DOC (Whyte et al., 2005)
- Rate of functional change during first two weeks was predictive of disability four months later (Whyte et al., 2005, 2009)
- Patients in VS who transition to MCS within 8 weeks of onset were more likely to continue recovering to higher levels of functioning one year after injury (Katz et al., 2009)
- Of individuals in VS or MCS at 1 year post injury, 0% of VS improved while 33% of MCS improved within 5 years post injury (Luaute et al., 2010)
- Patients with DOC who demonstrated visual tracking had better outcomes than those without (even >230 after admission), with earlier tracking associated with better outcome (Dolce, et al., 2010)
Predicting functional outcome after pediatric TBI: benefit of Time to Follow Commands above and beyond initial GCS score

<table>
<thead>
<tr>
<th></th>
<th>Discharge from inpatient rehab (n=120)</th>
<th>3 months after discharge from inpatient rehab (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>B</td>
</tr>
<tr>
<td>GCS</td>
<td>.08**</td>
<td>.10</td>
</tr>
<tr>
<td>TFC</td>
<td>.28***</td>
<td>-.52</td>
</tr>
<tr>
<td>PTA</td>
<td>.00</td>
<td>-.08</td>
</tr>
<tr>
<td>Overall model</td>
<td>R²=.37</td>
<td></td>
</tr>
</tbody>
</table>

Suskauer et al., JPRM, 2009
# Functional outcome at discharge from inpatient rehab for 120 children with TBI

Suskauer et al., JPRM, 2009

<table>
<thead>
<tr>
<th>Time to Follow Commands</th>
<th>No assistance needed</th>
<th>Set-up or supervision needed</th>
<th>Physical assist needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 days (n=41)</td>
<td>41%</td>
<td>37%</td>
<td>22%</td>
</tr>
<tr>
<td>3-11 days (n=43)</td>
<td>12%</td>
<td>49%</td>
<td>40%</td>
</tr>
<tr>
<td>12-26 days (n=27)</td>
<td>0%</td>
<td>44%</td>
<td>56%</td>
</tr>
<tr>
<td>&gt;26 days (n=9)</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Children with Severe TBI

- Hypotheses:
  - Injury severity would predict functional status at discharge
  - Functional status early in admission would predict status at discharge

- Included only children with lowest level of functioning at admission
  - WeeFIM raw score = 18

- Demographic, injury-related, and rehabilitation variables
  - WeeFIM scores collected at admission, 2-week intervals, discharge
WeeFIM

• Performance based assessment of functional independence in three domains:
  • Mobility, self-care, cognitive abilities
• Each scored from 1 (total assistance) to 7 (independent)
• 18 items; Raw score 18 – 126
• Developmental Quotient (DFQ)
  • Age corrected scores
  • % of age appropriate function
Sample Characteristics

- **Demographic**
  - $N = 35$
  - $M = 11$ (3 to 18)
  - 66% Male
  - 77% Caucasian

- **Injury/Rehabilitation**
  - GCS $M = 4.3$ (3 to 8)
  - Time from injury to rehab $M = 29$ days (5 to 117)
  - Length of rehab stay $M = 99$ days (14 to 255)

Interval assessment data

- **Month 1 data ($n=32$)**
  - $M = 19$ days from admission (range 12 to 27 days)

- **Month 2 data ($n=32$)**
  - $M = 34$ days from admission (range 29 to 44 days)
### Change or No Change?

<table>
<thead>
<tr>
<th>Any change by Month 1</th>
<th>Dependence at discharge</th>
<th>Partial Dependence at discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predictive power = 87.5%</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>No change by Month 1</th>
<th>Dependence at discharge</th>
<th>Partial Dependence at discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative predictive power = 62.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any change by Month 2</th>
<th>Dependence at discharge</th>
<th>Partial Dependence at discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predictive power = 85.0%</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No change by Month 2</th>
<th>Dependence at discharge</th>
<th>Partial Dependence at discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative predictive power = 83.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>70.0%</td>
<td>83.3%</td>
</tr>
<tr>
<td>89.5%</td>
<td>76.9%</td>
</tr>
</tbody>
</table>
3-Month Follow-Up Data

- Independence: DFQ > 85
- Partial Dependence: DFQ 30 - 84
- Dependence: DFQ < 30

DFQ Score

- Admission DFQ
- Month 1 DFQ
- Month 2 DFQ
- Discharge DFQ
- Follow-Up DFQ
Thank you. Questions?