Course Objectives

Upon completion of the course, participants will be able to:

2. Identify 2 requirements of operational strategies to support a comprehensive rehabilitation program for patients with disorders of consciousness.
3. List the 6 components of the Coma Recovery Scale-Revised used for assessment of persons with disorders of consciousness post brain injury.
4. Verbalize 4 of the Specialized Metrics considered in the administration guidelines for the Disorders of Consciousness COMPrehensive ASsessment battery (DOC COMPASS©), as discussed by the speaker.
5. Generate 3 examples of the clinical data compiled through the use of the DOC COMPASS© to evaluate treatment effectiveness for persons with disorders of consciousness.

Disorders of Consciousness 2016: The State of the Science

DoC State of the Science: Outline

- The problem of consciousness
- Assessment
  - Behavioral
  - Functional neuroimaging
- Prognosis and outcome
- Treatment

Disclosure

Dr. Giacino has no significant financial relationship with any commercial or proprietary entity that produces healthcare-related products and/or services relevant to the content of this presentation.

Dr. Giacino occasionally receives honoraria for conducting CRS-R training seminars.

Dr. Giacino receives grant funding from the National Institute of Neurological Disorders and Stroke, the National Institute on Disability, Independent Living and Rehabilitation Research, U.S. Department of Defense and the James S. McDonnell Foundation.
Disorders of Consciousness

**Coma**: A state of sustained pathologic unconsciousness in which the eyes remain closed and the patient cannot be aroused. (MSTF, NEJM, 1994)

**Vegetative State**: A condition in which there is complete absence of behavioral evidence for awareness of self and environment, with preserved capacity for spontaneous or stimulus-induced arousal (Aspen Workgroup, JHTR, 1997).

**Permanent VS**: A prognostic term that denotes an irreversible state which can be applied 12 months after a traumatic injury and after 3 months following non-traumatic injury in adults and children (AAN, Neurology, 1995).

**Minimally Conscious State**: A condition of severely altered consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated (Giacino, et al., Neurology, 2002).

Behavior = Gold standard

The Problem of Consciousness

“The limits of consciousness are hard to define satisfactorily and we can only infer the self-awareness of others by their appearance and their acts.”

Plum and Posner, 1982
*The Diagnosis of Stupor and Coma*

---

**Summary of Evidence Supporting Measurement Properties of Behavioral Assessment Scales for DOC**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Admin/Scoring</th>
<th>Reliability</th>
<th>Validity</th>
<th>Discriminative Ability</th>
<th>Construct</th>
<th>Criterion</th>
<th>Predictive Validity</th>
<th>Diagnostic Validity</th>
<th>Independent vs. Disability</th>
<th>Good vs. Disability and Death</th>
<th>Good/Mod Dis. vs. Severe Dis./PVS</th>
<th>Not predictive, 3 mos. Post injury</th>
<th>Not predictive, 6 months Post injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
<tr>
<td>INNS</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
<tr>
<td>RLS85</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
<tr>
<td>LOEW</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
<tr>
<td>CNC</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
<tr>
<td>DOCS</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
<tr>
<td>WHIM</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
<tr>
<td>SSAM</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
<tr>
<td>WNSSP</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
<tr>
<td>SMART</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
<tr>
<td>CRS</td>
<td>R</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
<td>Unproven</td>
</tr>
</tbody>
</table>

**Coma Recovery Scale- Revised**

<table>
<thead>
<tr>
<th>JCN CRINT RECOVERY SCALE- REVISED 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum score: 0</td>
</tr>
<tr>
<td>Scale measures the recovery from a state of severe brain injury</td>
</tr>
<tr>
<td>Levels of recovery range from severe to minimal</td>
</tr>
<tr>
<td>Each level is further divided into sublevels</td>
</tr>
<tr>
<td>Scores are corrected for age and sex</td>
</tr>
<tr>
<td>Scores can be used to track progress over time</td>
</tr>
</tbody>
</table>

(Adapted from Alshtul, et al. JNC in Ped Neurology, 2002)
Spaulding Rehabilitation Hospital

Coma Recovery Scale- Revised: Psychometric Characteristics

Coma Recovery Scale- Revised: Scaling Properties

LaPorta, et al., Arch Phys Med Rehabil, 2010

Coma Recovery Scale- Revised: Construct Validity

Coma Recovery Scale- Revised: Diagnostic Sensitivity/Specificity

Incidence of diagnostic error

37% (Childs et al. Neurol, 1993)
43% (Andrews et al. BMJ, 1996)
41% (Schnakers et al. Brain Injury, 2008)

Limitations of Behavioral Assessment

- Behavior is a poor proxy for conscious awareness
  - Eg, Cannot differentiate volitional from involuntary or reflexive movement (eg, smiling)
- May fail to detect co-existing sensory (eg, blindness), motor (eg, contractures) and cognitive impairments (eg, aphasia)
- Subject to subjective bias of examiner
  - No standard of care for examination procedures or response interpretation

(Giacino & Smart, Curr Opin Neurol, 2007)
Functional Neuroimaging Applications in DOC

Neurophysiologic heterogeneity in VS

Neurophysiologic heterogeneity in MCS

fMRI Studies of VS and MCS

Passive Paradigms
- Language processing
  - Familiar sounds
  - Words
  - Narratives
- Visual processing
  - Shapes
  - Pictures/Scenes
  - Faces

Active Paradigms
- Language comprehension
  - Command-following
- Movement
- Spatial navigation
- Pictures
- Communication
  - Yes/no imaging proxies

Detected Awareness in the Vegetative State

Discordant behavioral and neurophysiologic evidence of conscious awareness in an 18 y/o male s/p severe TBI (Rodriguez-Moreno, Schiff, Giacino et al, Neuron, 2010)

Schiff et al., Brain, 2002

(Owen & Coleman, Nat Rev Neurosci, 2009; Giacino, Hirsch, Schiff, Laureys, Arch Pk&R, 2006; Laureys, Owen, Schiff, Lancet, 2004)
Active fMRI Communication Paradigm

- 29 y/o male
- MVA (GCS =5)
- R frontal SDH/crani
- Remained in VS for 3.5 yrs
- Admitted to Liege for workup at 5yrs
- CRS-R/SMART found reproducible LE command-following but no behavioral evidence of communication
- fMRI communication paradigm showed 5/6 accurate yes/no responses

(Monti, et al., NEJM, 2012)

Resting State Networks:
DMN Connectivity in DoC


“MCS+ (plus)” v. “MCS- (minus)”

Electrophysiologic Approaches

Voluntary brain processing in disorders of consciousness

Can electromyography objectively detect voluntary movement in disorders of consciousness?

J Neurol Neurosurg Psychiatry, 2008

Voluntary brain processing in disorders of consciousness
The Perturbational Complexity Index (PCI):

The Multi-Society Task Force Report on Medical Aspects of the Persistent Vegetative State

"Recovery of consciousness after 12 months is unlikely in adults and children who have had traumatic injuries... Data were available on 434 patients in VS at one month after a severe head injury... Recovery after 12 months was reported in only 7 of the 434 patients."

Prognostic Guideline for the Vegetative State

Criteria for Permanence
- After 12 months following traumatic brain injury in adults and children
- After 3 months following non-traumatic brain injury in adults and children

(American Academy of Neurology, Neurol1995;45:1015-1018)

The Minimally Conscious State: Definition and Diagnostic Criteria
(Giacino, et al., Neurol 2002;58:349-53)

"The natural history and long-term outcome of MCS have not yet been adequately investigated... Although it is not known how many patients will emerge from MCS after 12 months after injury, most patients in MCS for this length of time remain severely disabled..."

- No prognostic guidelines established to date

When is MCS permanent?
Outcome from VS and MCS at 1 Year

VS = 54; MCS = 49; Mixed etiology; Mean time post-injury = 9 wks

Late Recovery from Vegetative State

Subjects: VS>6m (M=11m); Mixed etiology (n=50)

Longitudinal Outcome of Patients with Disorders of Consciousness in the TBI Model Systems


Treatment Interventions:

Neuromodulation

Intralaminar nuclei “reconnections” in spontaneous recovery from “vegetative” unresponsive state

Laureys et al, Lancet 2000

Thalamo-cortical connectivity and consciousness

A Multicenter Randomized Controlled Trial of the Effectiveness of Amantadine Hydrochloride in Promoting Recovery of Function Following Severe TBI

Primary Aims:

- Determine whether AH, given in a dose of 200 – 400 mg/day improves functional recovery from post-traumatic VS and MCS (4-16 wks post-injury).
- Determine whether AH-related gains in function persist following drug discontinuation

NIDRR Award # H133A031713
(Giacinto, Whyte, Bagiella, et al., NEJM, 2012)

Amantadine

Amantadine-induced facilitation of dopaminergic activity promotes enhanced neurotransmission to the dopamine-dependent nigrostriatal, mesolimbic, and frontostriatal circuits that are responsible for mediating arousal, drive, and attentional functions

Schindler et al, Neurol Neurosurg Psychiatry 2008
(Giacino et al, NEJM 2012)

A Multicenter Randomized Controlled Trial of the Effectiveness of Amantadine Hydrochloride in Promoting Recovery of Function Following Severe TBI

Primary Aims:

- Determine whether AH, given in a dose of 200 – 400 mg/day improves functional recovery from post-traumatic VS and MCS (4-16 wks post-injury).
- Determine whether AH-related gains in function persist following drug discontinuation

NIDRR Award # H133A031713
(Giacino, Whyte, Bagiella, et al., NEJM, 2012)
Discussion: Mechanism of Effect

- Improved dopamine availability may:
  - Restore tonic arousal, motor initiation, cognitive persistence and other behaviors mediated by dopamine-dependent fronto-striatal circuits
  - Preserve dysfunctional but viable neuronal populations in meso-limbic and frontal systems involved in attention and drive.

Relationship of lesion burden to outcome in cortical networks

Relationship of lesion burden to outcome in subcortical and brain stem structures

Conclusions

- Higher lesion burden on routine CT imaging is associated with worse recovery in patients with traumatic DoC.
- Some ROIs appear to have a more significant impact on recovery than others, but the specific regions contributing to unfavorable outcome remains uncertain.
- Lesion burden did not significantly limit the response to amantadine treatment, however, a decrease in rate of recovery was observed in the amantadine-treated group with highest lesion burden.
Zolpidem

Marked anterior forebrain hypometabolism is noted bilaterally in frontal/prefrontal cortex, thalami and striatum. Following zolpidem administration broad increases of metabolic rates are observed in these regions. (Brefel-Courbon, et al., AnnNeurol, 2007)

Thalamo-cortical connectivity and consciousness: Transcranial direct current stimulation (tDCS)

tDCS may increase neuronal excitability via facilitation of resting membrane action potential, spontaneous neuronal firing rates, synaptic strength and cerebral blood flow/metabolism through NMDA, calcium uptake or dopaminergic modulation. (Thibaut et al, Neurology 2014)

Central thalamic deep brain stimulation

Central lateral nucleus co-activates with anterior cingulate and SMA, nodes in the mesial frontal circuit that mediate response preparedness, motor intention and drive functions. (Schiff, Giacino, et al, Nature 2007)

Rationale for DBS in MCS

- Hallmark of MCS: Response inconsistency/impersistence
- Primary aim: To determine whether thalamic DBS can promote behavioral responsiveness and improve functional outcome in patients diagnosed with chronic MCS

Patient 1: Electrode placement

Central Thalamic Deep Brain Stimulation for Treatment of Chronic Post-Traumatic Minimally Conscious State

Design

- Double-blinded alternating crossover design

<table>
<thead>
<tr>
<th>Condition</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>ON</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OFF</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary Outcome Measure: Coma Recovery Scale - Revised

Frequency of best score on Arousal, Motor, and Communication subscales of CRS-R

Patient 1

- 33 y/o RH male
  - Blunt head trauma following assault resulting in b/l SDH (R>L)
  - 2 yrs inpatient rehab + 4 yrs nursing home
- Clinical status on re-admission (6.5 yrs post-injury):
  - Diagnosis: MCS
  - Inconsistent command-following
  - Rare single-word verbalization
  - Unable to communicate reliably or use common objects
  - Total care required, Unable to communicate with family/staff

Patient 1: Results

Behavioral Performance: Pre-DBS v. DBS On v. DBS Off

Conclusions

- DBS modulates specific cognitive and behavioral functions (arousal, functional limb movement, swallowing) via central thalamic upregulation of mesial frontal circuit (anterior cingulate and SMA).
Paradigms (re)framed by neuroimaging

**Summary**

- Disorders of consciousness exist along a dynamic continuum of residual cognitive function.
- Diagnostic error remains high among patients with DOC.
- Neuroimaging procedures may play a pivotal role in detecting conscious awareness in patients with concurrent sensory, motor, and cognitive deficits, but sensitivity and specificity must be carefully considered.
- Recent outcome studies suggest that individuals who sustain severe brain injury experience more substantial and longer periods of recovery than previously thought.
- Preliminary results support use of targeted neuromodulatory interventions aimed at facilitating recovery of specific cognitive and behavioral functions.