Disorders Of Consciousness ("DoC"):
An overview

Dmitry Esterov, D.O.
Department of Physical Medicine and Rehabilitation
Division of Brain Injury Rehabilitation
Mayo Clinic, Rochester MN
Learning Objectives

• Understand the latest guidelines from the 2018 American Academy of Neurology and ACRM guidelines, and Review 2020 ACRM DoC Position Statement.

• Classify the different types of disorder of consciousness patients and understand the importance of standardized assessments in this process.

• Summarize the recent evidence of imaging techniques for detecting brain activity and predicting recovery in persons with DoC.
practice guideline update recommendations summary: Disorders of consciousness

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research

Joseph T. Giacino, PhD, Douglas I. Katz, MD, Nicholas D. Schiff, MD, John Whyte, MD, PhD, Eric J. Ashman, MD, Stephen Ashwal, MD, Richard Barbano, MD, PhD, Flora M. Hammond, MD, Steven Laureys, MD, PhD, Geoffrey S.F. Ling, MD, Risa Nakase-Richardson, PhD, Ronald T. Seel, PhD, Stuart Yablon, MD, Thomas S.D. Getchius, Gary S. Gronseth, MD, and Melissa J. Armstrong, MD, MSc

Correspondence
American Academy of Neurology
guidelines@aan.com

Neurology® 2018;91:450-460. doi:10.1212/WNL.0000000000005926

Minimum Competency Recommendations for Programs That Provide Rehabilitation Services for Persons With Disorders of Consciousness: A Position Statement of the American Congress of Rehabilitation Medicine and the National Institute on Disability, Independent Living and Rehabilitation Research Traumatic Brain Injury Model Systems

Joseph T. Giacino, PhD, John Whyte, MD, PhD, Risa Nakase-Richardson, PhD, Douglas I. Katz, MD, David B. Arciniegas, MD, Sonja Blum, MD, PhD, Kristin Day, PT, PhD, Brian D. Greenwald, MD, Flora M. Hammond, MD, Theresa Bender Pape, DrPH, MA, CCC-SLP, Amy Rosenbaum, PhD, Ronald T. Seel, PhD, Alan Weintraub, MD, Stuart Yablon, MD, Ross D. Zafonte, DO, Nathan Zasler, MD
Introduction
Case Study

Case of Terry Wallis

“Man Wakes up to a Strange New World after 19 Years in Coma”
Terry Wallis

- DTI
- Images 18 months apart
- late reorganization of white matter connections and slow recovery of intraregional connectivity through axonal remodeling

More recent case study at Mayo Clinic

- 31 year old male from Minnesota sustained s/p Motorcycle collision on 10/13/20 associated with a large left subdural hematoma & midline shift s/p left hemicraniectomy and evacuation of subdural hematoma on 10/13/20.

- 10/19: “His DAI burden is graded as III due to involvement of the rostral midbrain, both fornices and diffusely through the corpus callosum. A 2017 study by Hamdeh et al. suggests that the anatomical grading of DAI correlates poorly to long-term neurological outcome, but the midbrain involvement and Duret hemorrhages in the periaqueductal gray matter are concerning. Given the patient's burden of diffuse axonal injury as well as his poor neurologic exam, his prognosis remains guarded.”

- Not seen by PM&R; PT/OT. SLP; seen by palliative medicine. Seen by SLP a few days prior to transfer to an LTAC on 10/30.

- “Waxing / waning rare command following”

- Remained admitted there until 12/6 where he re-presented to SMH for planned replacement of the cranial bone flap on 12/7/2020
Inpatient Rehabilitation – 12/17

• Started on Amantadine, stopped off Amantadine, then restarted
• Mirtazapine added
• Sympathetic Storming management
• Monitoring fevers / infections
• Spasticity management
• Neuro-optometry visiting with patient in the hospital
• With guidance from SLP, RT dropped cuff, trial PMV, Trach decannulated on 01/18 → much improved communication
• Bowel management / bladder management (terazosin)
• D/c home with PEG feeding
Outpatient Rehabilitation

- Multiple pain / musculoskeletal concerns
- Tapering / optimizing medications & Neurostimulants
- Botulinum toxin injections
- Manual custom wheelchair
- Re-evaluation with nutrition – removed PEG feeding
- Ongoing work with PT / OT / SLP
Current Function

- SLP: staying home alone for a few hours at a time; able to call his family when home alone without issue; simple external aids to support memory; takes out his phone without cueing when asked about what he did over the weekend and is able to describe pictures of recent events in his photos with several details included when provided with extra time. He shares that he took notes on his phone in OT, however, he needs intermittent cueing to locate the app on his phone.

- OT: consistently using the bathroom independently at home and continues to work on independent toileting in the community.

- PT: used a four-wheeled walker and ambulated 800 feet with min assist with walker

- Reports mood is good, feeling happy with his progress
  - He was spotted with his family enjoying concert
Questions raised from this case

• What might be outcome if patient did not receive intensive multidisciplinary rehabilitation?
• How many patients may not receive this level of care when they might make the same progress?
• How can we predict who will make this type of progress?
• What are the short term and long-term outcomes for those with severe TBI?
• How are decisions currently being made? How should decisions during early injury be made?
Overview of DoC

- Definitions
- Classification / Differentiating
- Clinical Assessment
Consciousness

• Defined as the state of awareness of self and environment
  • Arousal and awareness

• Severe acquired brain injury disrupts this arousal and awareness system, mediated by the brainstem and the cortex

• The most severe injuries can result in a prolonged state of a disorder of consciousness
Emergence from Consciousness:  
Current Definition - 2020

Full recovery of consciousness occurs when a person demonstrates either:

1) Reliable Communication
   - Accurate and consistent verbal or gestural yes/no responses

2) Functional Object Use
   - Demonstration of appropriate use of at least 2 common objects
## Definitions

<table>
<thead>
<tr>
<th>TABLE 32-1 Terms Used to Refer to Disorders of Consciousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akinetic mutism</td>
</tr>
<tr>
<td>Apallic syndrome</td>
</tr>
<tr>
<td>Coma</td>
</tr>
<tr>
<td>Coma vigil</td>
</tr>
<tr>
<td>Cognitive death</td>
</tr>
<tr>
<td>Decerebrate state</td>
</tr>
<tr>
<td>Low level</td>
</tr>
<tr>
<td>Minimally conscious state</td>
</tr>
<tr>
<td>Unresponsive wakefulness</td>
</tr>
</tbody>
</table>
DoC – General Classification Scheme

A) Coma
B) Vegetative State (VS); Unresponsive Wakefulness Syndrome (UWS)
C) Minimally Conscious State (MCS)
D) Emergence from MCS
### Coma vs. Brain Death

<table>
<thead>
<tr>
<th>Brain Death</th>
<th>Coma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complete loss of brain function</td>
<td>• Loss of spontaneous or stimulus induced arousal</td>
</tr>
<tr>
<td>• Including involuntary activity to sustain life</td>
<td>• Eyes remain continuously closed</td>
</tr>
<tr>
<td>• Implies permanent absence of cerebral AND brainstem functioning</td>
<td>• No evidence of sleep/wake cycles on electroencephalography</td>
</tr>
<tr>
<td></td>
<td>• Multiple mechanisms but underlying coma is broad withdrawal of excitatory synaptic activity across the cerebral cortex</td>
</tr>
</tbody>
</table>
Vegetative State → Unresponsive Wakefulness (UWS)

- Controversial name…

- Awareness of self and environment is presumed to be absent and there is no ability to interact with others

- Capacity for spontaneous or stimulus-induced arousal is preserved (eyes can open)

- Unresponsive wakefulness evidenced by sleep/wake cycles
  - There is opening of eyes (arousal) but with absent awareness largely because of thalamus / white matter cortex dysfunction.
### Coma vs. UWS

<table>
<thead>
<tr>
<th>Coma</th>
<th>UWS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Loss of spontaneous or stimulus induced arousal</td>
<td>• Eyes open spontaneously</td>
</tr>
<tr>
<td>• Eyes remain continuously closed</td>
<td>• + Evidence of sleep / wake cycles</td>
</tr>
<tr>
<td>• No evidence of sleep/wake cycles on electroencephalography</td>
<td></td>
</tr>
</tbody>
</table>

No awareness self or environment
Minimally Conscious State – “MCS”

• Definition: a condition of severely altered consciousness in which there is minimal, **intermittent, inconsistent**, but **definite** behavioral evidence of self or environmental awareness

• MCS + and MCS -  
  
  **Non linguistic signs** - object manipulation, localizing limb or eye movements

  **Signs of preserved language function**
  → command following, intelligible verbalization, intential communication
MINIMALLY CONSCIOUS STATE

MINIMALLY CONSCIOUS STATE +
- command following

MINIMALLY CONSCIOUS STATE -
- appropriate smiling/crying
- localization to noxious stimulation
- visual pursuit

VEGETATIVE STATE
- reflex movements
- eye opening

COMA

EMERGENCE
- functional communication and object use

Emergence from MCS

Recovery of consciousness occurs when a person demonstrates either:

• 1) Reliable Communication
  • Accurate and consistent verbal or gestural yes/no responses

• 2) Functional Object Use
  • Demonstration of appropriate use of at least 2 common objects
Differentiating ……

• What is accurate?
• What is consistent?
Diagnosing / Differentiating
- Complex!

• Estimated 40% inaccurate when clinician determines consciousness...

• Caveat

Differentiating / Diagnosing

- Medical Complications
- Language Impairment
- Motor Impairment
- Sensory Deficits
- Environmental Influences
Challenges in Differentiation

Differentiating Between States of Consciousness:
Why does it matter?

• Increasing evidence that patients diagnosed with MCS early in the course of recovery (i.e., within 3 months) achieve significantly more favorable functional outcomes by 12 months post injury compared with those diagnosed with UWS.

What is the Recommended Method for Differentiating?

Standardized Assessment Scales

• A systematic review performed by ACRM recommended:
  • JFK Coma Recovery Scale–Revised (CRS-R)
  • Wessex Head Injury Matrix
  • Sensory Modality Assessment and Rehabilitation Technique
  • Western NeuroSensory Stimulation Protocol
  • Disorders of Consciousness Scale

Coma Recovery Scale Revised

CRS - R

- International Gold Standard
- Requires training in performing
- **Specific** Tasks
- 6 subscales:
  - Hierarchically arranged, corresponding to brainstem $\rightarrow$ subcortical $\rightarrow$ cortical

<table>
<thead>
<tr>
<th>CRS - R</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Auditory function scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Consistent movement to command*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Reproducible movement to command*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Localization to sound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Auditory startle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visual function scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Object recognition*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Object localization: reaching*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Visual pursuit*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Fixation*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Visual startle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Motor function scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Functional object use†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Automatic motor response*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Object manipulation*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Localization to noxious stimulation*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Flexion withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Abnormal posturing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>None/flaccid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oromotor/verbal function scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Intelligible verbalization*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Vocalization/oral movement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Oral reflexive movement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Communication scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Functional: accurate†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Nonfunctional: intentional*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arousal scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Eye opening without stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Eye opening with stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Unarousable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates a minimally conscious state.
† Indicates emergence from the minimally conscious state.
## Communication Assessment Protocol ©2004

### Situational Orientation

<table>
<thead>
<tr>
<th>Visually Based</th>
<th>Aurally Based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am I touching my ear right now? (do not touch ear)</td>
<td>Am I clapping my hands right now? (do not clap)</td>
</tr>
<tr>
<td>Am I touching my nose right now? (touch nose)</td>
<td>Am I clapping my hands right now? (clap)</td>
</tr>
<tr>
<td>Am I touching my nose right now? (touch nose)</td>
<td>Am I clapping my hands right now? (clap)</td>
</tr>
<tr>
<td>Am I touching my ear right now? (do not touch ear)</td>
<td>Am I clapping my hands right now? (do not clap)</td>
</tr>
<tr>
<td>Am I touching my nose right now? (do not touch nose)</td>
<td>Am I clapping my hands right now? (clap)</td>
</tr>
<tr>
<td>Am I touching my ear right now? (touch ear)</td>
<td>Am I clapping my hands right now? (do not clap)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>of 6</td>
</tr>
<tr>
<td></td>
<td>of 6</td>
</tr>
<tr>
<td></td>
<td>of 6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>of 6</td>
</tr>
<tr>
<td></td>
<td>of 6</td>
</tr>
<tr>
<td></td>
<td>of 6</td>
</tr>
</tbody>
</table>

©2020 MFMER | slide 30
Clinicians caring for individuals with DoC should perform serial standardized assessments to identify trends in trajectory of recovery important for prognosis.
Overview of DoC

- Epidemiology
- Medical Decision Making
- Outcomes
- Prediction
Epidemiology of DoC

“Most deaths after severe traumatic brain injury occurred after withdrawal of life-sustaining therapy and that the rate of withdrawal of life-sustaining therapy varied significantly across level one trauma centers.

This raises the concern that differences in mortality between centers may be partly due to variation in physicians’ perceptions of long-term prognosis and physicians’ practice patterns for recommending withdrawal of life-sustaining therapy.”
• JAMA Neurology 2021

• 2058 (12%) had a DOC after completion of acute care treatment; By completion of inpatient rehabilitation, 414 of 17,470 patients (2%) had a DOC.

• TBIMS – referral bias
• JAMA Neurology 2021; TRACK TBI (acute phase to 12 months post injury)
• Outcome measured by Glasgow Outcome Scale Extended
Long Term Outcomes

Natural History

- Studies of the Traumatic Brain Injury Model Systems (TBIMS) cohort have shown that of 396 TBIMS participants who were admitted to inpatient rehabilitation unable to follow commands:
  - 268 (68%) regained command-following;
  - Of these, 91 (23%) emerged from post-traumatic amnesia prior to rehabilitation discharge
  - Of those who had failed to recover command-following by rehabilitation discharge, the majority of those with follow-up were able to follow commands by post-injury Years 1 (59%; n=46/78), 2 (66%; n=31/47), and 5 (74%; n=25/34).
  - Of 337, 20% were living without in-house supervision, and 19% were competitively employable.

Nakase Richardson, 2012. Longitudinal Outcome of Patients with Disordered Consciousness in the NIDRR TBI Model Systems Programs
Prognosis – summary from ACRM article

• “Recent evidence indicates that approximately 30%-40% of persons admitted to IRF in VS/UWS or MCS recover functionally important behaviors such as consistent command-following, intelligible speech, and reliable communication prior to discharge.

• Long-term outcome studies demonstrate that at least 20% go on to attain independence in community and vocational activities within 5 years of injury.

• The total proportion achieving independence increases further by 10 years post injury.”
Can we predict outcome early after TBI?

- Emerging evidence suggests that covert consciousness, or cognitive motor dissociation (CMD), is present in up to 15–20% of patients with DoC and that detection of CMD in the intensive care unit can predict functional recovery at 1 year post injury.

- CMD is characterized by volitional brain activity detected by task-based functional MRI or EEG in a patient whose bedside behavioral diagnosis suggests coma, UWS, MCS-

Edlow 2021; Nature Reviews, Neurology; Mar;17(3):135-156. doi: 10.1038/s41582-020-00428-
Adrian M. Owen – “The Search for Consciousness”
Functional Neuroimaging

Early detection of consciousness in patients with acute severe traumatic brain injury

Brian L. Edlow,¹,²,³,* Camille Chatelle,¹,²,⁴,* Camille A. Spencer,² Catherine J. Chu,² Yelena G. Bodien,¹,²,⁵ Kathryn L. O’Connor,² Ronald E. Hirschberg,⁵,⁶ Leigh R. Hochberg,¹,²,⁷ Joseph T. Giacino,⁵,⁶ Eric S. Rosenthal²,# and Ona Wu³,#
Reproducibility

- Meta analysis of 30+ studies, 1000+ patients – about 15-25% can detect “covert consciousness”

### Table 3

<table>
<thead>
<tr>
<th>Active paradigms</th>
<th>Command following</th>
<th>No command following</th>
<th>Total</th>
<th>Per cent</th>
<th>Command following</th>
<th>% No command following</th>
<th>Total</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS</td>
<td>42</td>
<td>250</td>
<td>292</td>
<td>14.4%</td>
<td>66</td>
<td>180</td>
<td>246</td>
<td>26.8%</td>
</tr>
<tr>
<td>MCS</td>
<td>98</td>
<td>205</td>
<td>303</td>
<td>32.0%</td>
<td>74</td>
<td>275</td>
<td>349</td>
<td>21.2%</td>
</tr>
<tr>
<td>MCS vs VS: OR 2.85 (95% CI 1.9 to 4.2; p=0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EEG vs fMRI: OR 0.73 (95% CI 0.50 to 1.07; p=0.112)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Recommendations regarding Prognosis

When discussing prognosis with caregivers of patients with a DoC during the first 28 days postinjury, clinicians must avoid statements that suggest these patients have a universally poor prognosis (Level A).

*Long-term functional outcome defies accurate prognostication early after brain injury*
2018 Guidelines - Classification

• Prolonged DOC - > 28 days
• Permanent VS is not justified

• Should be replaced by chronic UWS (to indicate stability of the condition)

“Chronic Phase” → 12 months after TBI; 3 months after non-traumatic BI.
Medical Management

Medical Complexity
Paroxysmal Sympathetic Hyperactivity
Treatment
Medical Complexity; Medical Complications

Study of 194 patients, within 6 months post injury, 188 of 194 patients (>95%) developed at least 1 MC and 142 of them (73%) showed at least 1 severe MC.

Respiratory complications were most often due to pulmonary infections (65%), tracheal stenosis or malacia (22%). Among muscular / cutaneous complications, spasticity was the most frequent (80%), followed by pressure ulcers (56%), fractures (10%), and arthritis (8%). Endocrine-metabolic disorders often consist of low serum albumin level (42%), diabetes mellitus (32%), thyroid gland dysfunction (26%), anemia.
Paroxysmal Sympathetic Hyperactivity

- Paroxysmal Sympathetic Hyperactivity
  - hyperthermia, tachycardia, tachypnea, hypertension, diaphoresis, and posturing, occurring in “paroxysms”
  - DDx: Constipation / UTI / Infx, wounds, HO, Fx, DVT, Resp Distress, wounds

<table>
<thead>
<tr>
<th>PSH Treatments</th>
<th>Mechanism of Action</th>
<th>Dosing</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha Agonists</strong>&lt;br&gt;Clonidine</td>
<td>Alpha 2 agonist</td>
<td>0.1 - 0.3 mg q8hrs</td>
<td>Hypotension / bradycardia</td>
<td>Use is primarily for prevention</td>
</tr>
<tr>
<td><strong>Beta Blockers</strong>&lt;br&gt;<strong>Propranolol</strong>&lt;br&gt;Metoprolol&lt;br&gt;Labetalol</td>
<td>Beta Blockers</td>
<td>20 - 60mg q4-6hrs&lt;br&gt;25 mg q 8hrs&lt;br&gt;100 - 200mg q12hr</td>
<td>Hypotension, bradycardia, bronchospasm / hypoglycemia (propranolol)</td>
<td>Caution in COPD, respiratory disease, heart block.&lt;br&gt;Propranolol may lower mortality</td>
</tr>
<tr>
<td><strong>Opioids</strong>&lt;br&gt;Morphine&lt;br&gt;Fentanyl</td>
<td>Mu opioid receptor agonist</td>
<td>1 - 10mg prn&lt;br&gt;Patch can be 25 - 75 mcg q72hrs</td>
<td>Respiratory depression, sedation, hypotension</td>
<td>Helps to prevent and abort paroxysms</td>
</tr>
<tr>
<td><strong>Neuromodulators</strong>&lt;br&gt;Gabapentin&lt;br&gt;Bromocriptine&lt;br&gt;Baclofen</td>
<td>α2δ presynaptic Ca Channel&lt;br&gt;Dopamine agonist&lt;br&gt;GABA B agonist</td>
<td>100 - 300mg q8 h&lt;br&gt;- 1.25 mg q12hrs (up to 40mg / day)&lt;br&gt;- 5mg q8hrs (up to 80mg / day)</td>
<td>Sedation&lt;br&gt;Dyskinesia, hypotension&lt;br&gt;Sedation, elevated LFTs, weakness</td>
<td>With bromocriptine, can lower seizure threshold.&lt;br&gt;Avoid abrupt discontinuation with baclofen</td>
</tr>
<tr>
<td>PSH Treatments</td>
<td>Mechanism of Action</td>
<td>Dosing</td>
<td>Adverse Effects</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------</td>
<td>--------</td>
<td>----------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Peripherally Acting</strong>&lt;br&gt;Dantrolene</td>
<td>Interferes with Calcium release from sarcoplasmic reticulum</td>
<td>0.25 - 2mg / kg (max dose 10 mg/kg/d), every 6 - 12 hours</td>
<td>Liver toxicity, respiratory depression</td>
<td>Avoid in active liver disease / monitor LFTs before and during treatment</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong>&lt;br&gt;Clonazepam</td>
<td>GABA A Agonist</td>
<td>0.5 - 0.8 mg</td>
<td>Sedation, hypotension, respiratory depression</td>
<td>Used for treatment, may worsen cognitive status and neurologic recovery</td>
</tr>
</tbody>
</table>

Treatment - Sensory Stimulation

• Most are non controlled designs or descriptive single cases

• A few small RCT / crossover design studies with Familiar Auditory Sensory Training (FAST)

Physical Stimulation

• 50 participants following TBI

• Primary outcome - CRS-R

• Randomized to conventional tilt table or treatment with a tilt table with an integrated robotic stepping device

• Both improved compared to baseline, but CRS-R was better after conventional treatment

Neuromodulation - Amantadine

A double-blind, randomized, placebo-controlled, international multicenter study

Highest level of evidence for the use of Amantadine in promoting recovery after TBI
6 weeks and included 184 vegetative state or MCS subacute patients randomly assigned to receive Amantadine or placebo

Neuromodulation - Zolpidem

• 2 large studies (2009 and 2014)

• 1 of 15 patients (6.7%) and 4 of 84 patients (4.8%), respectively, had a significant and reproducible improvement on the JFK Coma Recovery Scale–Revised with 10mg of Zolpidem,

• Other SPECT / PET scan studies showed increased blood flow after Zolpidem reduction of inhibitory tonic activity

Transcranial Direct Current Stimulation (tDCS)

- 16 patients, randomized, double blind
- Sham vs. actual tDCS

Thilbault 2014
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study</th>
<th>Number of participants and cause of DoC</th>
<th>Time since injury</th>
<th>Diagnosis</th>
<th>Study design</th>
<th>Procedure</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep brain stimulation (DBS)</td>
<td>Schiff et al.</td>
<td>1 TBI</td>
<td>6 years</td>
<td>1 MCS</td>
<td>Single-subject, double-blind, alternating crossover</td>
<td>Bilateral electrical DBS of the central thalamus; CRS-R assessments performed during DBS 'on' and 'off' periods</td>
<td>Increased frequency of cognitively mediated behaviour; functional limb control and oral feeding, during 'on' periods</td>
<td>Proof of principle that stimulation of the central thalamus can lead to cognitive and functional gains in patients with chronic DoC</td>
</tr>
<tr>
<td>Transcranial direct current stimulation</td>
<td>Thibaut et al.</td>
<td>3 non-TBI, 2 TBI</td>
<td>1 week–10 years</td>
<td>25 V5/ LWS, 10 MCS</td>
<td>Double-blind, sham-controlled, crossover</td>
<td>Single session (20 min) of stimulation and sham over the left DLPCF, with CRS-R, before and after stimulation</td>
<td>In 13 participants with MCS and 2 participants with VS/UWS, the CRS-R score was higher after stimulation than before stimulation; no side effects</td>
<td>Proof of principle that non-invasive stimulation of DLPCF can lead to cognitive gains</td>
</tr>
<tr>
<td>Repetitive transcranial magnetic stimulation</td>
<td>Cincotta et al.</td>
<td>9 non-TBI, 2 TBI</td>
<td>9–85 months</td>
<td>11 V5/ LWS</td>
<td>Double-blind, crossover</td>
<td>Five sessions of 20-Hz stimulation or sham for 10 min, for a total of 1,000 pulses delivered in 5 trains, over the left primary motor cortex for 5 consecutive days; EEG and CRS-R performed before and after stimulation</td>
<td>No change in behavioural or EEG measurements; no side effects</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Vagal nerve stimulation</td>
<td>Corazzoli et al.</td>
<td>1 TBI</td>
<td>15 years</td>
<td>1 V5/UWS</td>
<td>Single-subject</td>
<td>Stimulation (up to 1.5 mA intensity) administered over 6 months, with CRS-R, EEG and FDG PET performed before and after stimulation</td>
<td>After 1 month of stimulation, the participant transitioned from VS to MCS and EEG showed increased theta power; after 3 months of stimulation, PET showed increased metabolic activity in the thalamus, basal ganglia and multiple regions of the cerebral cortex</td>
<td>Proof of principle that vagal nerve stimulation can lead to modulation of cortical activity and clinical improvement in chronic VS/UWS</td>
</tr>
</tbody>
</table>
What factors or procedures help to predict outcome?

• "Amantadine probably hastens functional recovery in patients with MCS or VS/UWS secondary to severe TBI over 4 weeks of treatment (moderate confidence in the evidence, 1 Class I study) and appears safe in this population”

• “In patients with VS/UWS of mixed etiologies, conventional tilt table treatment is probably superior to tilt table treatment incorporating an integrated stepping device (moderate confidence in the evidence based on 1 Class I study), but the benefit vs placebo not established”
Summary and Final Recommendations from Article

Minimum Competency Recommendations for Programs That Provide Rehabilitation Services for Persons With Disorders of Consciousness: A Position Statement of the American Congress of Rehabilitation Medicine and the National Institute on Disability, Independent Living and Rehabilitation Research Traumatic Brain Injury Model Systems

Joseph T. Giacino, PhD, John Whyte, MD, PhD, Risa Nakase-Richardson, PhD, Douglas I. Katz, MD, MD, David B. Arciniega, MD, Sonja Blum, MD, PhD, Kristin Day, PT, PhD, Brian D. Greenwald, MD, Flora M. Hammond, MD, Theresa Bender Pape, DrPH, MA, CCC-SLP, Amy Rosenbaum, PhD, Ronald T. Seel, PhD, Alan Weintraub, MD, Stuart Yablon, MD, Ross D. Zafonte, DO, Nathan Zasler, MD

Practice guideline update recommendations summary: Disorders of consciousness

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research

Joseph T. Giacino, PhD, Douglas I. Katz, MD, Nicholas D. Schiff, MD, John Whyte, MD, PhD, Eric J. Aschner, MD, Stephen Ashwal, MD, Richard Barbano, MD, PhD, Flora M. Hammond, MD, Steven Laurens, MD, PhD, Geoffrey S.F. Ling, MD, Risa Nakase-Richardson, PhD, Ronald T. Seel, PhD, Stuart Yablon, MD, Thomas S.J. Getchius, Gary J. Gromet, MD, and Melissa J. Armstrong, MD, MSc

Neurology® 2019;93:450-460. doi:10.1212/WNL.0000000000006926

Correspondence
American Academy of Neurology
guidelines@aan.com
Recommendation 1

“Clinicians should refer patients with DoC who have achieved medical stability to settings staffed by multidisciplinary rehabilitation teams with specialized training to optimize diagnostic evaluation, prognostication, and subsequent management, including effective medical monitoring and rehabilitative care (Level B).”

Davidson GH, Hamlat CA, Rivara FP, Kopesell TD, Jurkovich GJ, Arbabi S. Long term Survival of Adult Trauma Patients. JAMA, March 9, 2011—Vol 305, No. 10
Recommendation 1

- Significant medical complications slow recovery and interfere with treatment interventions.
- In view of this risk, patients are likely to have a better chance for recovery if care is provided in a specialized setting managed by clinicians knowledgeable about DoC.
- Large retrospective trauma registry found that cumulative mortality at 3 years post discharge is significantly lower for patients discharged to home or inpatient rehabilitation facilities than those discharged to skilled nursing facilities, even after adjusting for covariates.

Recommendation 2

- Importance of using standardized assessment scales
- Serial Exams / Increasing Arousal
- Awareness of Confounding disorders
- Clinicians may use multimodal evaluations including functional imaging and electrophysiological techniques to assess for covert consciousness**

- **2020 AAN European Guideline recommend task-based fMRI and EEG to be performed “whenever feasible”
Other recommendations

• Clinicians should avoid statements regarding a universally poor prognosis within the first 28 days of injury
• Clinicians should perform standardized behavioral assessments to inform prognosis
• The term “permanent VS” should be discontinued
• Once in chronic UWS phase and prolonged DoC, counselling should be advised on likelihood of permanent disability and need for long term assistive care; importance of goals of care discussions
• Patient and family preferences must be identified early
Treatment Statements - Summary

- Discussions should be had between family and provider
- Assessment and understanding of medical complexity and care
- Accurate assessment of pain is difficult; should treat pain if there is a reasonable cause (note assessments of pain in DoC are being studied)
- Amantadine between 4 and 16 weeks of injury
- Discussion about off-label uses / lesser studied modalities
Minimum Competency Recommendations for Programs That Provide Rehabilitation Services for Persons With Disorders of Consciousness: A Position Statement of the American Congress of Rehabilitation Medicine and the National Institute on Disability, Independent Living and Rehabilitation Research

Traumatic Brain Injury Model Systems

Joseph T. Giacino, PhD, a John Whyte, MD, PhD, b Risa Nakase-Richardson, PhD, c Douglas I. Katz, MD, d,e David B. Arciniegas, MD, f Sonja Blum, MD, PhD, g Kristin Day, PT, PhD, h Brian D. Greenwald, MD, i Flora M. Hammond, MD, j Theresa Bender Pape, DrPH, MA, CCC-SLP, k,l Amy Rosenbaum, PhD, m,n Ronald T. Seel, PhD, o Alan Weintraub, MD, p,q Stuart Yablon, MD, r Ross D. Zafonte, DO, s Nathan Zasler, MD, t,u
Key Points

• Behavioral Assessment (CRS-R) is the gold standard
• Assessing for confounding factors
• Treatment with multidisciplinary brain injury specialists
• Understanding and Treating high rate of medical complications
• Amantadine & Zolpidem
• Assistive technology assessment
• Incorporating errorless and procedural learning strategies even if patient still in PTA*
• Structure disposition plan, caregiver education

Barriers

- Admission policies and cost-control measures imposed by payors have limited access to comprehensive rehabilitation for patients who have DoC.
- IRF contingent on documentation of rapid functional improvement.
- Reimbursement to SNFs is typically insufficient to support multidisciplinary rehabilitation and specialty medical monitoring.
- LTC / SNF options are limited as well.
Conclusions

• Tremendous progress currently being done and active research internationally, but mechanisms essential for recovery are yet to be fully elucidated

• Reliable prognostic tools are lacking at each stage of recovery, and recovery of consciousness can occur at any time across the temporal spectrum of DoC

• Behavioral examination remains gold standard

• *Clinicians should consider all possible diagnostic, prognostic, and therapeutic approaches to support recovery in patients with DoC*
About Curing Coma®

In 2019 the Neurocritical Care Society launched Curing Coma® as its signature clinical, scientific, and public health effort. Curing Coma® is the first global public health initiative to tackle the unifying concept of coma as a treatable medical entity. The goal of Curing Coma® is to develop and implement coma treatment strategies that improve human lives. Click here to learn more, and click here to get involved today!

COME-TOGETHER Coma Care Survey

Treatment practices and attitudes regarding prognosis of coma vary widely across the world. To better understand prevailing concepts and the full spectrum of this variability, the NCS Neurocritical Care Research Network (NCRN) is conducting the COME-TOGETHER survey on coma epidemiology, evaluation, and therapy.
Thank you!!

If further questions, please reach out:

Esterov.Dmitry@mayo.edu