

# Practice Guidelines for Management of Patients with Disorders of Consciousness

## Report of the AAN-ACRM-NIDILRR Guideline Development Panel

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# Disclosure

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Dr. Giacino has no financial interest to disclose.

# Guideline Sponsorship, Funding and Endorsement

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This practice guideline was *endorsed* by the American Academy of Physical Medicine and Rehabilitation, American College of Surgeons Committee on Trauma, and Child Neurology Society.

# Objective

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- To present updated care recommendations for diagnosis, prognosis, outcome and treatment of patients with prolonged disorders of consciousness (DoC)
  - Prolonged:  $\geq 28$  days post-injury
- Specific Aim: To update the 1995 AAN PVS guideline and the 2002 MCS case definition.

*Note: This presentation will focus on selected recommendations*

**MEDICAL ASPECTS OF THE PERSISTENT VEGETATIVE STATE (First of Two Parts)**

Tom Michael's Special Task Force on PVS\*

**Abstract** This consensus statement of the Multi-Society Task Force summarizes current knowledge of the medical aspects of the persistent vegetative state in adults and children.

The vegetative state is a clinical condition of complete unresponsiveness of the self and the environment, accompanied by sleep-wake cycles, with either complete or partial preservation of hypothalamic and brainstem autonomic functions. In addition, patients in a vegetative state show evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or nociceptive stimuli; show no evidence of language comprehension; have bowel and bladder incontinence, and have variably preserved cranial nerve and spinal reflexes. We define persistent vegetative state as a vegetative state present one month after acute traumatic or nontraumatic brain injury or lasting for at least one month in patients with degenerative or metabolic disorders or developmental malformation.

**special article**

**Practice parameters: Assessment and management of patients in the persistent vegetative state (Summary statement)**

Report of the Quality Standards Subcommittee of the American Academy of Neurology

"The term 'persistent vegetative state' was coined by J. Jennett and Plum in 1972 to describe the condition of patients with severe brain damage in whom coma has progressed to a state of wakefulness without appreciable awareness. Such patients have sleep-wake cycles but no ascertainable cerebral cortical function. Jennett and Plum thought that patients in a persistent vegetative state could be distinguished clinically from those with other conditions associated with prolonged unconsciousness.

In 1983 the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research accepted the definition of persistent vegetative state proposed by Jennett and Plum and defined consciousness as the inability "to experience the environment." In the commission's judgment, a person with a persistent vegetative state is not conscious. It is important to recognize that patients are not in the vegetative state, even before a complete and permanent loss of consciousness. The term "persistent vegetative state" is applied only after a complete and permanent loss of consciousness has been established. The commission's report states that "patients in a persistent vegetative state are not conscious, but they are not in a permanent vegetative state."

A comprehensive literature review from 1972 to 1993 of all MEDLINE references using the terms

**special article**

NEUROLOGY 1995;45:1015-1034

**Recommendations for Use of Uniform Nomenclature Pertinent to Patients With Severe Alterations in Consciousness**

American Congress of Rehabilitation Medicine

**Abstract:** American Congress of Rehabilitation Medicine. Recommendations for use of uniform nomenclature pertinent to patients with severe alterations in consciousness. *Progress, Arch Phys Med Rehabil* 1995;76:285-9.

There continues to be considerable confusion and controversy among medical professionals concerning the use of uniform nomenclature pertinent to patients with severe alterations in consciousness. This is a uniform classification system that is based on behaviorally determined recommendations for defining persistent vegetative state, minimally responsive state, and locked-in syndrome brain features. Current controversies surrounding use of these terms also apply to patients with severe alterations in consciousness.

1995 by the American Congress of Rehabilitation Medicine

Each year, the number of survivors of severe brain injury increases. Improvements in critical care management and rehabilitative treatment are primarily responsible for the decrease in mortality rates that has occurred in the last 15 years. Although many of these survivors will achieve significant recovery of function, as many as 30% to 40% will remain in prolonged states of severely reduced consciousness throughout their lives. This is a uniform classification system that is based on behaviorally determined recommendations for defining persistent vegetative state, minimally responsive state, and locked-in syndrome brain features. Current controversies surrounding use of these terms also apply to patients with severe alterations in consciousness.

They are particularly relevant for their activities

**special article**

**POSITION PAPER**

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Because of the nature of these injuries, patients with severe alterations in consciousness often remain in these states for long periods of their lives. This is a uniform classification system that is based on behaviorally determined recommendations for defining persistent vegetative state, minimally responsive state, and locked-in syndrome brain features. Current controversies surrounding use of these terms also apply to patients with severe alterations in consciousness.

They are particularly relevant for their activities

**Development of Practice Guidelines for Assessment and Management of the Vegetative and Minimally Conscious States**

The Aspen Neurobehavioral Conference was convened to develop guidelines for the assessment and management of the vegetative and minimally conscious states. The purpose of this conference was to develop a uniform classification system that is based on behaviorally determined recommendations for defining persistent vegetative state, minimally responsive state, and locked-in syndrome brain features. Current controversies surrounding use of these terms also apply to patients with severe alterations in consciousness.

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**History**

**Special Article**

**The minimally conscious state**

Definition and diagnostic criteria

J.T. Giacino, PhD, S. Ashwal, MD, N. Childs, MD, B. Cranford, MD, B. J.P. Kelly, MD, J.H. Rosenber, MD, J. Whyte, MD, PhD, R.D. Zafra

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**Comprehensive systematic review update**

**summary: Disorders of consciousness**

Report of the Guideline Development, Dissemination, and Subcommittee of the American Academy of Neurology, the Rehabilitation Medicine, and the National Institute on Disability and Rehabilitation Research

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**Articles**

**Comprehensive systematic review update summary: Disorders of consciousness**

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# Prior Guidelines

Guideline	VS	MCS
Diagnosis	Yes	Yes
Prognosis	Yes	No
Natural history	Yes	No
Treatment	No	No

# What's new since 2002?

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- Estimates of misdiagnosis among patients with DoC consistently approximate 40% in both US and European studies.
- Diagnostic and prognostic applications of functional neuroimaging electrophysiological procedures emerge.
- Natural history studies extend follow-up beyond 1 year.
- Multicenter randomized controlled interventional trials completed.

# Clinical Questions

## Question 1

- What procedures accurately diagnose prolonged DoC ( $\geq 28$  days)?

## Question 2

- What is the natural history of prolonged DoC?

## Question 3

- What factors or procedures help to predict outcome in prolonged DoC?

## Question 4

- What treatments are effective for prolonged DoC?

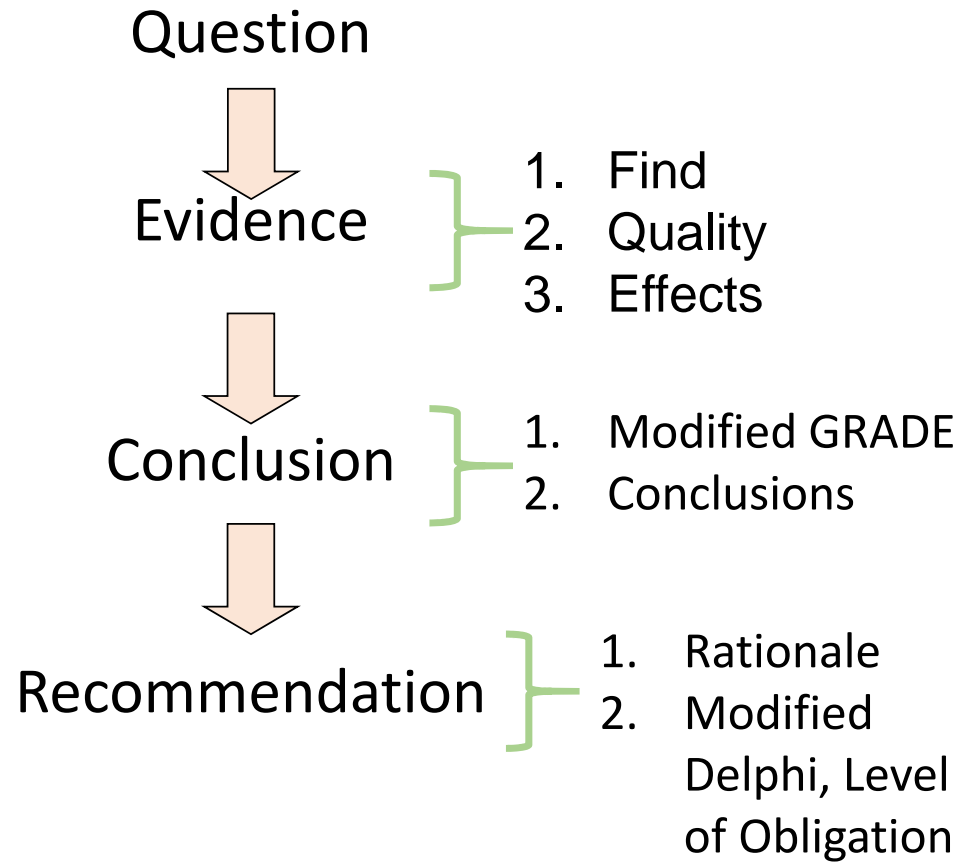


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# Approach to the Analysis of the Evidence

# Evidence-Based Process

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# Literature Search

Rigorous, Comprehensive, Transparent

**21,677**  
abstracts

**608** full  
text reviews

**371** rated  
articles

Databases (1950-2017): MEDLINE, Science Citation Index, EMBASE (searches 2012, 2015, 2017)

## Inclusion criteria:

- Population had a DoC for at least 28 days from date of injury
- Minimum of 20 patients with prolonged DoC (a priori decision)
- Answered guideline question

## Exclusion criteria:

- Case reports
- Expert opinion/consensus
- Studies not examining patients with a prolonged DoC

# Assessing Quality & Synthesizing Evidence

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- Grading quality of studies – risk of bias
  - High (Anchor two Class I)
  - Moderate (Anchor two Class II)
  - Low (Anchor two Class III)
  - Very low (Anchor < one Class III)
- Key general criteria for high quality studies
  - Prospective
  - Inclusion criteria clearly defined
  - At least 80% of enrolled subjects have outcome measured
  - Masked or objective outcome assessment
  - Substantively equivalent baseline characteristics between groups or appropriate statistical adjustment



# Level of Obligation

Level	Obligation	Confidence in Evidence	Degree of Consensus	Acceptance of Principles	Confidence in Related Evidence
A	Must	High	100%	100%	100%
B	Should	Moderate	≥ 80% to < 100%	≥ 80% to < 100%	≥ 80% to < 100%
C	May	Low	≥ 50% to < 80%	≥ 50% to < 80%	≥ 50% to < 80%
D	No Recommendation	Very Low	< 50%	< 50%	< 50%

# Recommendation Development

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- Evidence +
- *Rationale based on:*
  - Systematic review evidence
  - Strong related evidence
  - Principles of care
  - Inferences from other premises
- *Level of obligation anchored in:*
  - Rationale, Benefits/Harms
  - Modifiers: (1) availability, (2) patient financial burden, (3) variation in patient preferences, (4) importance of outcomes
- *Modified Delphi process for consensus*

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# Recommendations for Diagnostic Assessment



# Practice Recommendations

## Recommendation Statement 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**).

# Practice Recommendations

- Recommendation 1 Rationale

- *Rate of misdiagnosis high* (confounding neurologic deficits, co-morbid medical complications, examiner inexperience, instability of condition)
- *Knowledge gaps* often lead to overestimation or underestimation of prognosis by non-specialists.
- *Accurate diagnosis important* to educate (level of consciousness, prognosis, treatment decisions)
- *Related Evidence:* Cumulative mortality at 3 years post-discharge significantly lower for patients discharged to inpatient rehabilitation facilities or home v. skilled nursing facilities, after adjusting for covariates (*Davidson et al, JAMA, 2011*).

# Practice Recommendations

## Recommendation 2a

- Clinicians should *use standardized neurobehavioral assessment measures* that have been shown to be valid and reliable (such as those recommended by the ACRM) to improve diagnostic accuracy for the purpose intended (**Level B** based on importance of outcomes and feasibility).

# Practice Recommendations

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## Recommendation 2a Rationale

- Difficult to distinguish volitional from random/nonpurposeful behavior
- Unrecognized sensory (e.g. blindness), motor (e.g. weakness) and cognitive (e.g. aphasia) impairments may mask conscious awareness.

# Recommended DoC Assessment Scales

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- Standardized evaluation scales: (recommended with minor or moderate reservations)
  - The Coma Recovery Scale-revised (CRS-R)
  - The Sensory Modality Assessment Rehabilitation Technique (SMART)
  - Sensory Stimulation Assessment Measure
  - The Western Neuro Sensory Stimulation Profile
  - Wessex Head Injury Matrix
  - Disorders of Consciousness Scale (DOCS)

(Seel et al., Assessment scales for DOC, *Arch Phys Med Rehabil*, 2010)

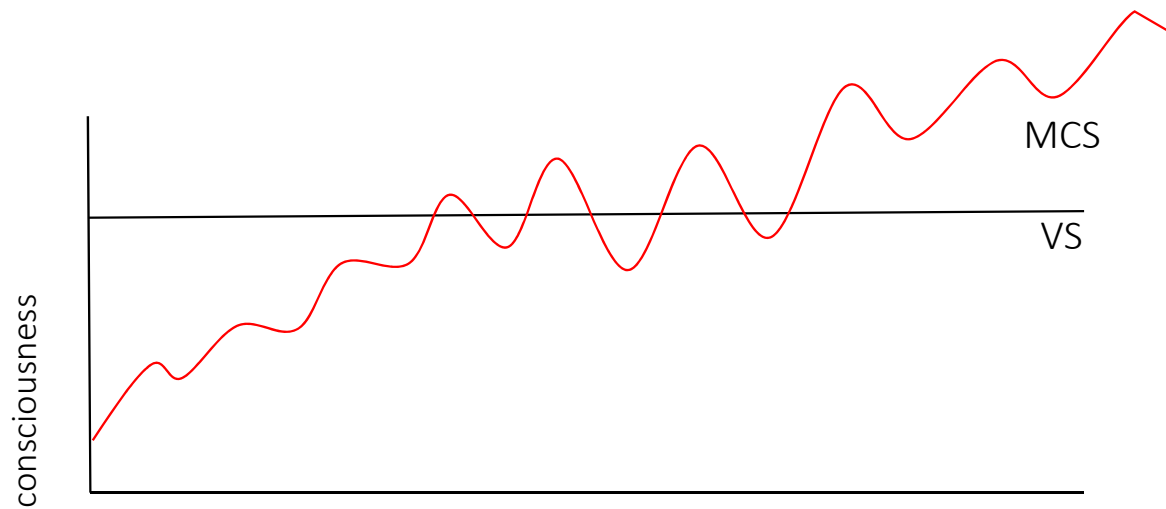
# Practice Recommendations

## Recommendation Statement 2b

- To reduce diagnostic error in individuals with prolonged DoC after brain injury, *serial standardized neurobehavioral assessments* should be performed with the interval of reassessment determined by individual clinical circumstances (Level B based on cogency, feasibility, and cost relative to benefit).

# Recommendation 2b Rationale

- Fluctuations in level of consciousness



# Practice Recommendations

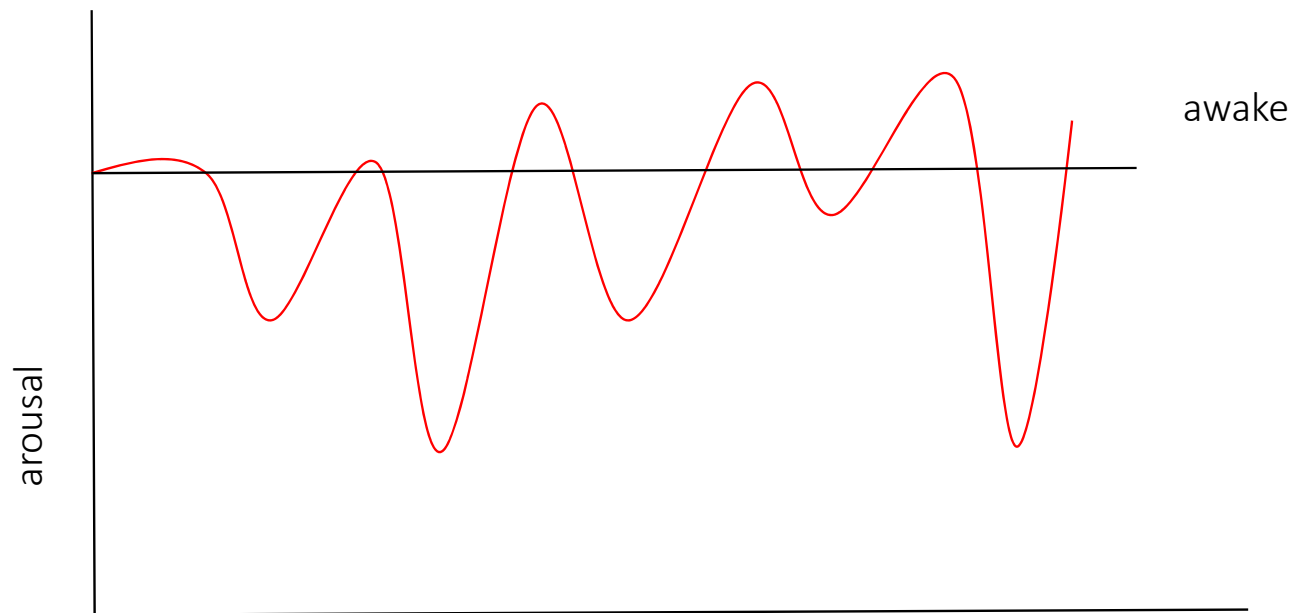
## Recommendation Statement 2c

- Clinicians should attempt to *increase arousal* before performing evaluations to assess level of consciousness anytime diminished arousal is observed or suspected (**Level B** based on importance of outcomes).



# Recommendation 2c Rationale

- Reduced or fluctuating level of arousal



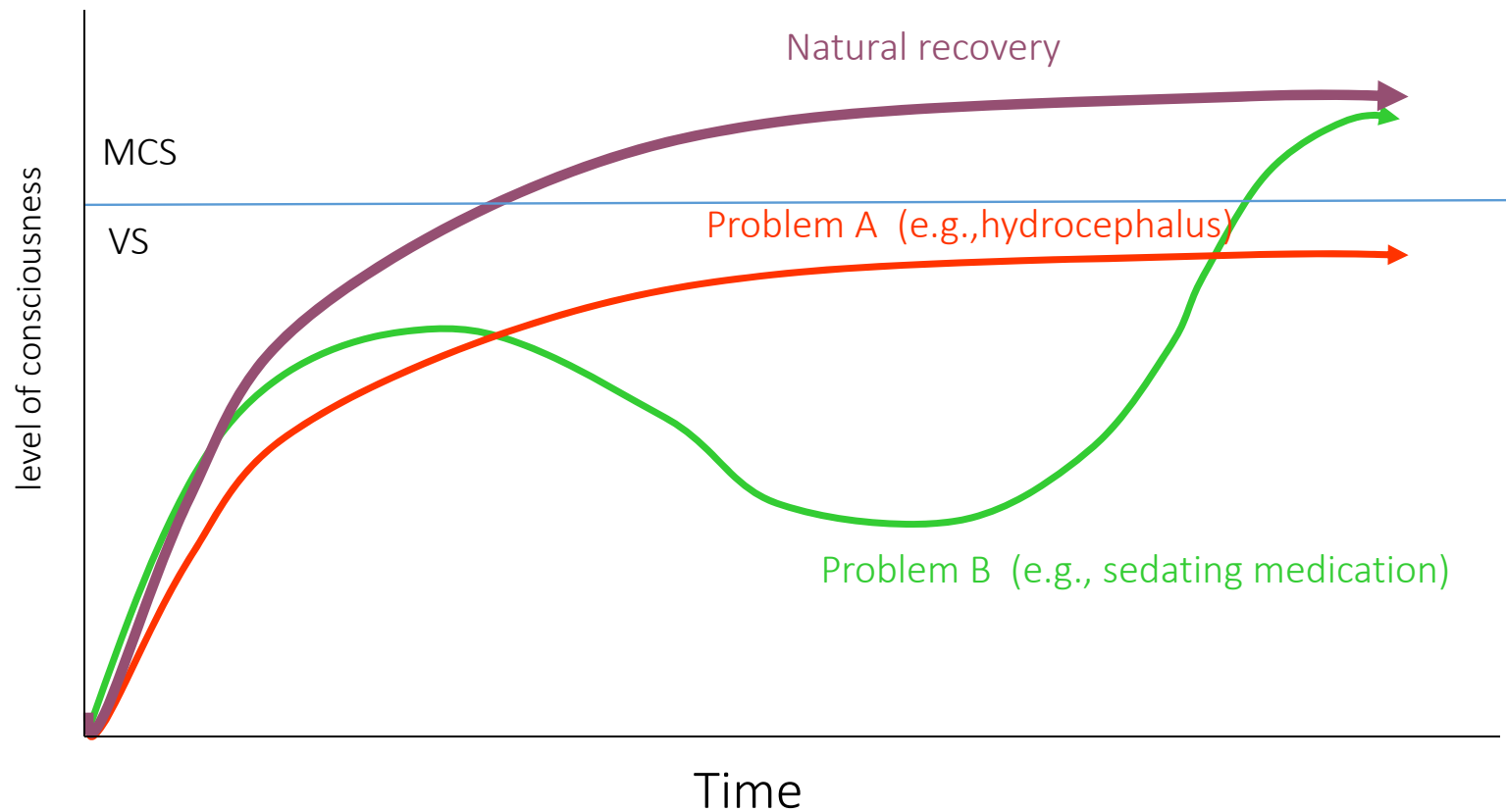
# Practice Recommendations

## Recommendation Statement 2d

- Clinicians should *identify and treat conditions* that may confound accurate diagnosis of a DoC prior to establishing a final diagnosis (**Level B** based on feasibility and cost).

# Recommendation 2d Rationale

- Complications and adverse effects of medications and environment that may compromise responsiveness



# Practice Recommendations

## Recommendation Statement 2e

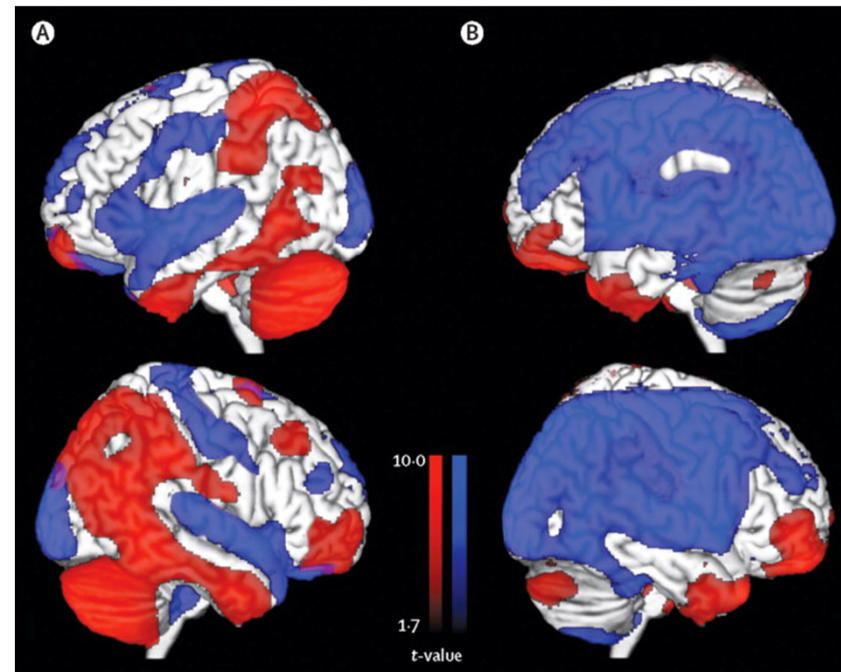
- *In situations where there is continued ambiguity* regarding evidence of conscious awareness despite serial neurobehavioral assessments, or *where confounders to a valid clinical diagnostic assessment are identified*, clinicians may use multimodal evaluations incorporating specialized functional imaging or electrophysiologic studies to assess for evidence of awareness not identified on neurobehavioral assessment that might prompt consideration of an alternate diagnosis (**Level C** based on assessment of benefit relative to harm, feasibility, and cost relative to benefit).

# Recommendation 2e Rationale

- PET better sensitivity than fMRI in detecting MCS (Stender et al., *Lancet*, 2014)
  - *FDG PET*: 93% sensitivity (CI 85-98); congruence with CRS-R: 85%
  - *fMRI*: 45% sensitivity (CI 30-61); Congruence with CRS-R 63% [*only 50% of patients could be assessed by fMRI*]

Statistical  
parametric  
mapping analysis  
of FDG PET

MCS



VS

# Recommendation 2e Rationale

- Neurophysiologic techniques: EMG, EEG, EP
  - *EMG response to command*: Distinguished levels of consciousness possibly more sensitive than behavioral measures. [*Low confidence in the evidence due to precision; likelihood ratio [LR+] 23.0, 95% confidence interval [CI] 1.5–355.6*] (Lesenfants et al., Neurology, 2016; Habbal et al., Brain Injury, 2014)
  - *EEG reactivity* to at least one type of sensory stimulus: Distinguishes MCS from VS to a mildly important degree. [*Low confidence in the evidence due to precision; LR+ 2.00, 95% CI 1.43–2.80*] (Estraneo et al., Clin Neurophysiol, 2016)
  - *Sensory evoked potentials* to nociceptive stimulus: presence of N2P2 in all MCS but <1/2 VS [*Low confidence in the evidence due to precision; LR+ 2.30, 95% CI 1.43–3.67*] (Naro et al., PLoS One, 2015)
  - *Pertubational Complexity Index (PCI) Index*: TMS and high density EEG source modeling showed loss of effective connectivity in VS, preserved in MCS, LIS and controls [*Low confidence in the evidence due to precision; LR+ 3.375, 95% CI 1.87–6.09*] (Cassarotto et al., Ann Neurol, 2016; Casali et al., Science Trans Med, 2013; Rosanova et al., Brain, 2012)

# Practice Recommendations

## Recommendation Statement 2f

- *In situations where there is no behavioral evidence of consciousness on clinical examination but functional neuroimaging or electrophysiologic testing suggests the possibility of preserved conscious awareness, frequent neurobehavioral reevaluations may be conducted to identify emerging signs of conscious awareness (Level C based on feasibility) and decisions to reduce the intensity of rehabilitation treatment may be delayed for those individuals receiving active rehabilitation management (Level C based on variation in patient preferences and cost relative to net benefit), with the length of time over which these are done determined by an agreement between the treating clinician and the health care proxy given the lack of evidence to provide guidance.*

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# Recommendations Regarding Natural History and Prognosis



# Practice Recommendations

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## Recommendation Statement 3

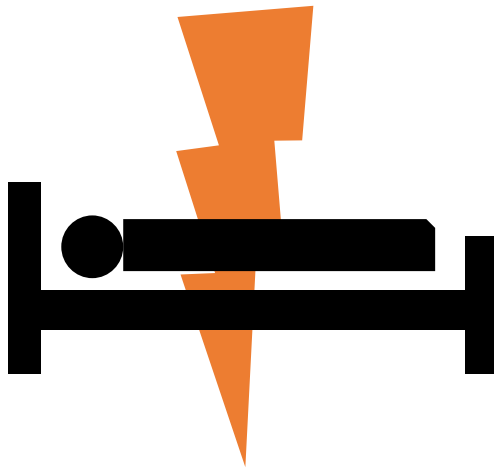
- When discussing prognosis with caregivers of patients with a DoC during the first 28 days post injury, clinicians *must avoid statements that suggest these patients have a universally poor prognosis (Level A)*.

# Etiology informs prognosis

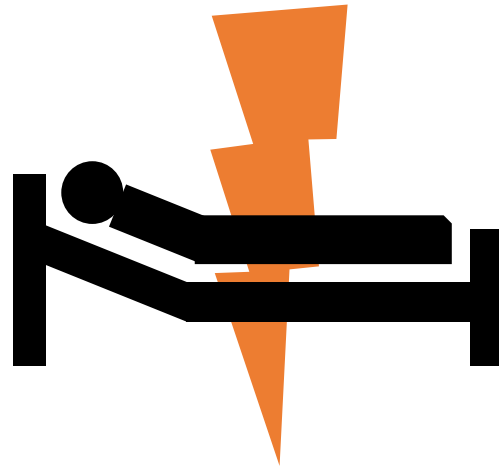
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## Traumatic

VS/UWS



MCS

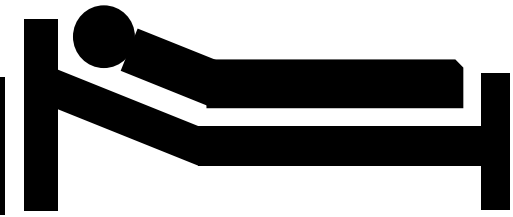


## Non-traumatic

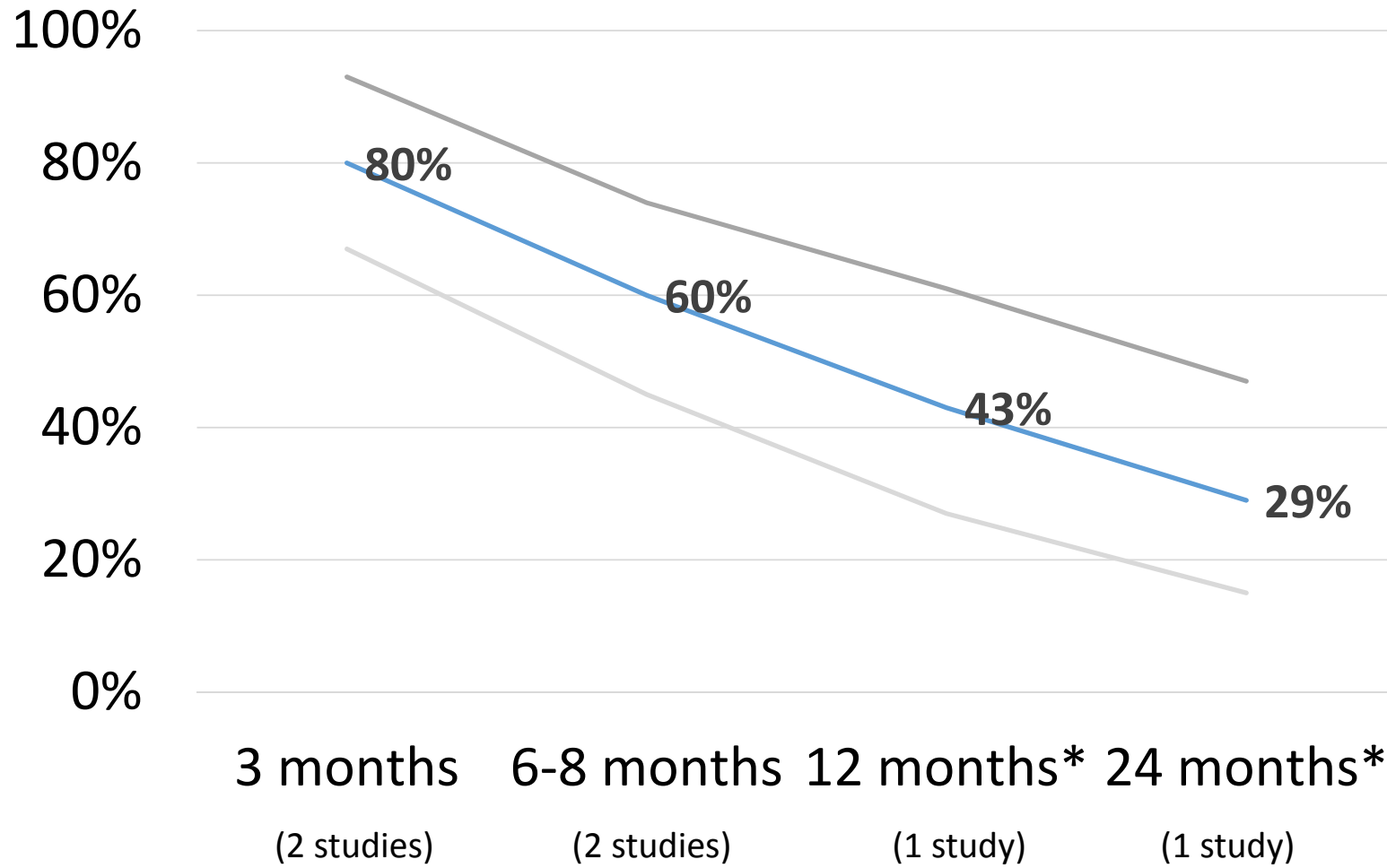
VS/UWS



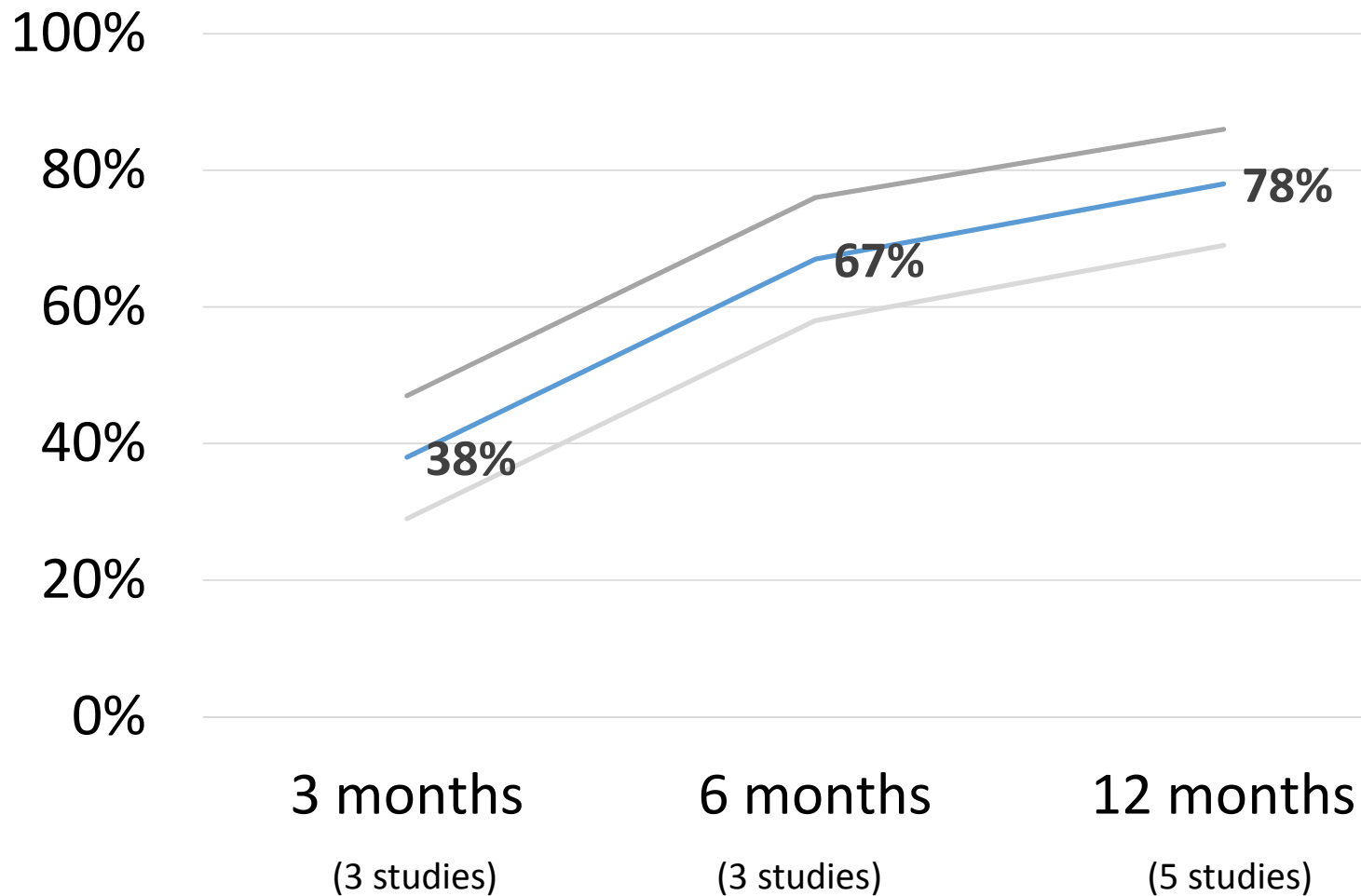
MCS



## ***Survival*** of Patients with Prolonged ***Non-Traumatic VS/UWS***



# Percent *Recovery of Consciousness* in Patients with Prolonged *Traumatic VS/UWS*



**Recovery of Consciousness:**  
Development of behavior suggesting awareness of self or environment, emergence from VS to MCS

- Limitations:***
1. Insufficient evidence to draw conclusions regarding frequency of other outcomes (e.g. disability)
  2. No studies investigated natural history recovery of this cohort >12 months

## Percent *Recovery of Consciousness* in Patients with Prolonged *Non-traumatic VS/UWS*

Time	Recovery of Consciousness	Caveat
By 6-8 months	17% (5% - 30%)	3 studies; meta-analysis includes patients 6- and 8-months post-insult
Between 6-24 months	7.5% (0%-24%)	Estimate for patients still in a DoC at 6 months Meta-analysis of 2 studies published 20 years apart (1993 and 2013), with high heterogeneity in the meta-analysis

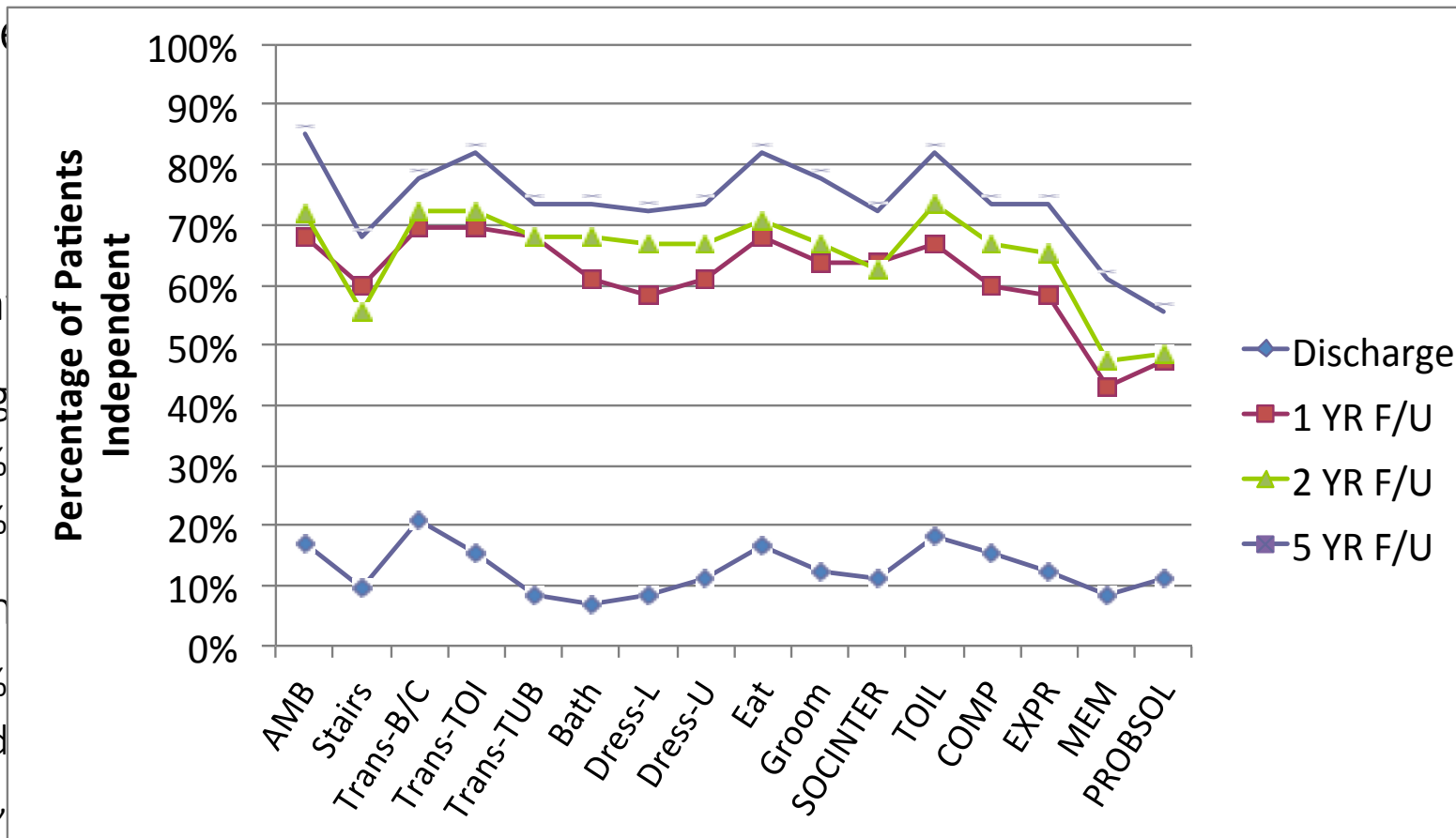
# Rationale Recommendation 3

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- Withdrawal of life-sustaining treatment (WoLST) is a common cause of death for patients with severe TBI
  - TBI population: 70% of hospital deaths due to WoLST; 65% within 72 hrs of injury (*Turgeon 2011 CMAJ*)

# Percent *Recovery of Function* in Patients with Prolonged Traumatic VS/UWS/MCS

- TBI Model enrolled
- Media
- Evaluation
- During
  - 68%
  - 23%
- Amort
  - 21%
  - 63 d
  - 1, 2,



(Wheeler, et al, Richardson, et al, J Neurotrauma 2012 29:59-65)

# Practice Recommendations

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## Recommendation Statement 7

- Given the frequency of recovery of consciousness after 3 months in patients in nontraumatic VS/UWS, and after 12 months in patients with traumatic VS/UWS (including some cases emerging from MCS) *use of the term permanent VS should be discontinued.*
- After these time points, *the term chronic VS (UWS) should be applied, accompanied by the duration of the VS/UWS* (Level B).



# Rationale Recommendation 7

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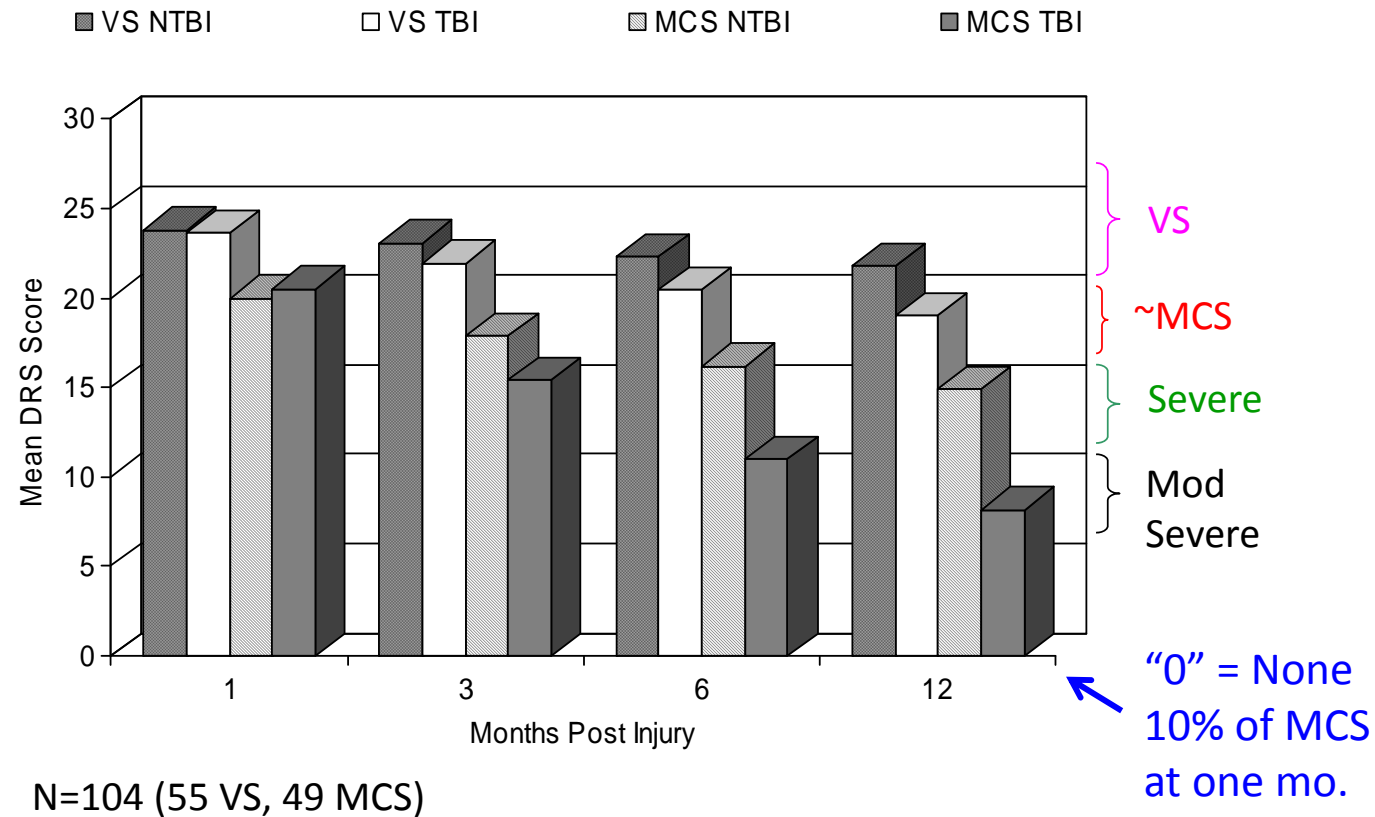
- Late transition to MCS from VS/UWS may occur in as many as 20% of patients who meet permanence criteria (*Estraneo, et al, Neurol, 2010*)
- ≈20% with late recovery will regain ability to communicate reliably, perform self-care activities, interact socially but most will remain severely disabled (*Whyte, et al, Arch Phys Med Rehabil, 2010*)

# Practice Recommendations

## Recommendation Statement 8

- Clinicians should counsel families that *MCS diagnosed within 5 months of injury and traumatic etiology are associated with more favorable outcomes* and *VS/UWS and nontraumatic DoC etiology are associated with poorer outcomes*, but individual outcomes vary and prognosis is not universally poor (Level B based on importance of outcomes).

# Rationale Recommendation 8



- *Age and length of time post-injury not supported as prognostic features.*

*(Giacino J, Kalmar K, Journal of Head Trauma Rehabil, 1997)*

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# Recommendations Related to Treatment

# Practice Recommendation

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## Recommendation Statement 12

- Clinicians should *be vigilant to the medical complications* that commonly occur during the first few months after injury among patients with DoC and, thus, should *utilize a systematic assessment approach to facilitate prevention, early identification, and treatment* (Level B).

# Rationale Recommendation 12

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- Complications frequent in early stages and require specialized expertise
  - Most common: Urinary tract infection, hypertonia, sleep disturbance, agitation.
  - Most serious: Hydrocephalus, pneumonia, and paroxysmal sympathetic hyperactivity (require acute hospitalization).
  - Contribute to mortality, morbidity, rehabilitation treatment interruption, and cost.
- Early recognition of risk of complications and care protocols designed for prevention and rapid management may reduce adverse outcomes

# Practice Recommendation

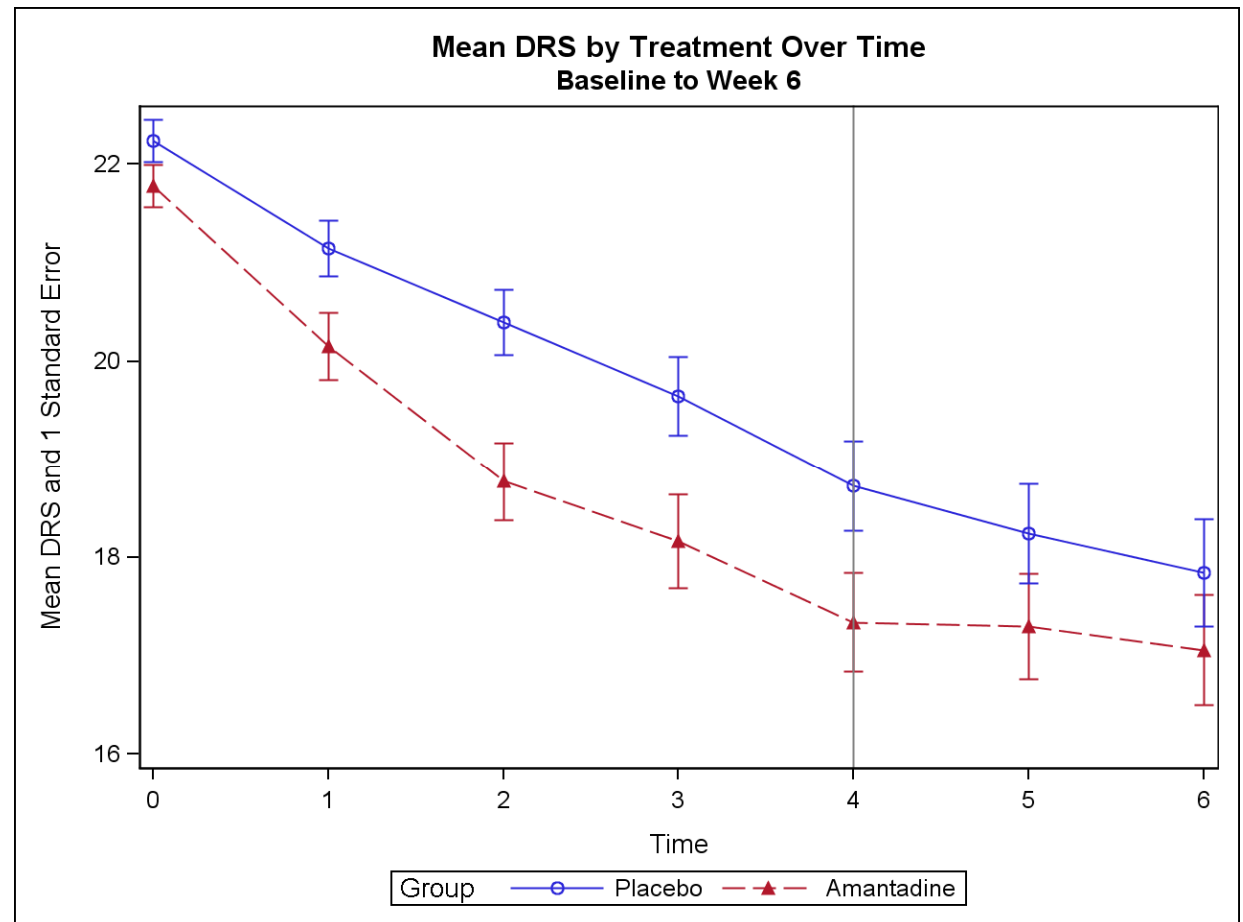
## Recommendation Statement 14

- Clinicians caring for patients with traumatic VS/MCS who are between 4 and 16 weeks post injury should *prescribe amantadine* 100-200 mg twice daily to hasten functional recovery and reduce degree of disability in the early stages of recovery *after determining there are no medical contraindications* or other case-specific risks for use (Level B).

# Rationale Recommendation 14

- Class I RCT compared Amantadine HCl to placebo
  - TBI
  - VS & MCS
  - Ages 16 – 65
  - 4 – 16 weeks post-injury
  - 100 – 200 mg BID X 4 weeks
  - Washout X 2 weeks
- Significantly faster recovery during treatment (DRS)
- Significantly slower recovery during washout
- No differences in adverse events
- Long-term impact of treatment unclear

*(Giacino, Whyte, et al, NEJM, 2012)*





# Practice Recommendations

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## Recommendation Statement 15

- Clinicians should counsel families about the *limitations of existing evidence* concerning treatment effectiveness and the *potential risks and harms* associated with interventions that lack evidentiary support (Level B).

# Rationale Recommendation 15

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- Caregivers frequently in crisis
  - Overwhelmed by the magnitude and unfamiliarity of event
  - Vulnerable to unsupported claims of treatment benefit
  - Overly-optimistic and likely to adopt a “nothing to lose” attitude (even when substantial chance of natural recovery remains)
- Clinicians have limited ability to disentangle natural from treatment-induced recovery in the individual patient

# Practice Recommendation

## Recommendation Statement 15 (cont.)

- When discussing non-validated treatments, clinicians should *provide evidence-based information regarding the projected benefits and risks* of a particular treatment and *discuss the level of uncertainty* associated with the proposed intervention, keeping in mind that families and caregivers are often in distress and vulnerable (Level B).

# Practice Recommendation

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## Recommendation Statement 15 (cont.)

- Clinicians should counsel families that, in many cases, it is impossible to discern whether improvements observed early in the course of recovery were caused by a specific intervention or spontaneous recovery (**Level B**).

# Limitations and Gaps

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## Diagnosis

- Absence of strong reference/gold standard complicates calculation of sensitivity and specificity.
- Inattention to masking procedures introduces bias and threatens validity.

## Prognosis

- Failure to stratify participants by diagnostic and etiologic subtypes and to anchor outcome assessment to date of injury contributes to imprecise outcome projection.

## Treatment

- Absence of control group and small sample size limit ability to account for differences in treatment effect related to mediating factors (eg, chronicity, comorbidities).
- Short length of stay disincentivizes family members to enroll patients in placebo-controlled trials in view of 50% likelihood of assignment to the placebo arm.

