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NIDILRR

National Institute on Disability, Independent Living,
and Rehabilitation Research

Update: Disorders of Consciousness

Report by:

Guideline Development, Dissemination, and Implementation Subcommittee
of the American Academy of Neurology

Evidence in Practice Committee of the American Congress of Rehabilitation Medicine
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Presentation Objectives

- To present an updated systematic review of the evidence since the 1995 AAN practice parameter on persistent vegetative state (PVS) and the 2002 case definition of minimally conscious state (MCS)
- To present updated care recommendations for patients with prolonged disorders of consciousness (DoC)

Overview

- Introduction
- Clinical questions
- AAN guideline process
- Methods
- Conclusions
- Practice recommendations

Introduction

- Severe acquired brain injury is a catastrophic event that can result in prolonged (i.e., lasting at least 28 days) DoC, including the vegetative state (VS)² and MCS.³
 - Table e-1 of the published guideline provides the definitions for VS and MCS and other key terms pertinent to DoC.
- As shown by available epidemiologic data,⁸ the annual US incidence of VS is approximately 4,200 persons. The incidence of MCS is unknown.
- Obtaining accurate prevalence figures for VS/UWS and MCS in the United States is hampered by economic factors that lead patients with DoC to be transferred from the acute care setting to long-term care facilities where they are often lost to follow-up.
- The cost of lifetime care for persons with prolonged DoC can exceed \$1,000,000.⁶
- In 1995, the AAN published diagnostic and prognostic guidelines for PVS⁷ following an evidence-based review completed by the Multi-Society Task Force (MSTF) on PVS.² In 2002, the Aspen Neurobehavioral Workgroup defined MCS and published consensus-based diagnostic criteria.³
- Following publication of the MCS definition, the pace of research on DoC accelerated and new evidence has become available.

Introduction

- Published estimates of misdiagnosis among patients with DoC consistently approximate 40% in both US and European studies.¹³⁻¹⁵
- Underlying visual or motor impairments interfering with detection of command-following and failure to detect visual pursuit are frequent causes of failure to detect consciousness.
- The rate of diagnostic error underscores the need for more refined evaluation methods.
- Natural history studies of patients with prolonged DoC now include outcomes extending beyond 1 year.
- Now is an opportune time to reevaluate current approaches to assessment and clinical care.

Introduction

- The purpose of this systematic review and accompanying guideline is to update the 1995 AAN PVS guideline⁷ and the 2002 MCS case definition.³
- This review aimed to answer 10 clinical questions (see table e-2 of the published guideline) which can be summarized in 4 overarching questions concerning patients with traumatic and nontraumatic DoC:
 - What procedures accurately diagnose prolonged DoC (prolonged DoC is defined as lasting at least 28 days)?
 - What is the natural history of prolonged DoC?
 - What factors or procedures help to predict outcome in prolonged DoC?
 - What treatments are effective for prolonged DoC?

Clinical Questions

Question 1

- What procedures accurately diagnose prolonged DoC (prolonged DoC is defined as lasting at least 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?

AAN Guideline Process*

- Clinical Question



- Evidence



- Conclusions



- Recommendations

*Guideline developed using the 2011 *AAN Clinical Practice Guideline Process Manual*, as amended

Literature Search/Review

Rigorous, Comprehensive, Transparent

21,677
abstracts



371 rated
articles

Three databases were searched: MEDLINE (1950–2012), Science Citation Index (1960–2012), and EMBASE (1980–2012); search was updated in November 2015 and again in February 2017



Inclusion criteria:

- Population had a DoC for at least 28 days from date of injury
- Minimum of 20 patients with prolonged DoC enrolled
- Minimum sample size selected a priori

Exclusion criteria:

- Case reports
- Studies relying solely on expert opinion or consensus
- Articles not relevant to the clinical questions
- Articles unrelated to the disease topic or scope
- Studies not examining patients with a prolonged DoC

AAN Classification of Evidence (2004)

Diagnostic Accuracy Scheme

Class I

- A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient's clinical status. Study results allow calculation of measures of diagnostic accuracy.

Class II

- A case-control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared with a broad spectrum of controls, or a cohort study with a broad spectrum of persons with the suspected condition where the data were collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.

AAN Classification of Evidence (2004)

Diagnostic Accuracy Scheme

Class III

- A case-control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy.

Class IV

- Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

AAN Classification of Evidence (2004)

Prognostic Accuracy Scheme

Class I

- A cohort study of a broad spectrum of persons at risk for developing the outcome (e.g., target disease, work status). The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class II

- A case-control study of a broad spectrum of persons with the condition compared with a broad spectrum of controls, or a cohort study of a broad spectrum of persons at risk for the outcome (e.g., target disease, work status) where the data were collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

AAN Classification of Evidence (2004)

Prognostic Accuracy Scheme

Class III

- A case-control study or a cohort study where either the persons with the condition or the controls are of a narrow spectrum where the data were collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy.

Class IV

- Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

AAN Classification of Evidence (2004)

Screening Scheme

Class I

- A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

Class II

- A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

AAN Classification of Evidence (2004)

Screening Scheme

Class III

- A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician.

Class IV

- Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

AAN Classification of Evidence (2011)

Therapeutic Scheme

Class I

A clinical RCT of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:

- a. Concealed allocation
- b. No more than two primary outcomes specified
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
- e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following characteristics are also required*:
 - i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
 - ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).
 - iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
 - iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.
- f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate.

* Note that numbers I to iii in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

AAN Classification of Evidence (2011)

Therapeutic Scheme

Class II

An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets items b–e (see Class I).

(Alternatively, a randomized crossover trial missing one of the following two characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.)

All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

AAN Classification of Evidence (2011)

Therapeutic Scheme

Class III

- All other controlled trials (including studies with external controls such as well-defined natural history controls).
- (Alternatively, a crossover trial missing both of the following two criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.)
- A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV

- Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Clinical Question 1

- What procedures accurately diagnose prolonged DoC (prolonged DoC is defined as lasting at least 28 days)?

Clinical Question 1: Diagnostic Assessment

Conclusions

- **Electromyography (EMG)**

- In patients with a DoC for at least 28 days, a positive EMG response to command using a threshold of 1.5 on a ratio between a response to motor commands and a control command to distinguish voluntary responses from involuntary movements is possibly helpful in distinguishing patients with MCS from those with VS/UWS (likelihood ratio [LR+] 23.0, 95% confidence interval [CI] 1.5-355.6).
 - Low confidence in the evidence, 1 Class I study³⁴ with decreased confidence in the evidence due to precision

- **EEG**

- It is possible that EEG reactivity to at least one type of sensory stimulus distinguishes MCS from VS to a mildly important degree.
 - Low confidence in the evidence; 1 Class I study³¹ with decreased confidence in the evidence due to precision; LR+ 2.00, 95% CI 1.43-2.80

Clinical Question 1: Diagnostic Assessment

Conclusions

- ***Evoked Potentials***

- It is possible that the presence of A δ -fiber laser-evoked potential (LEP) N2P2 and C-fiber LEP N2P2 components in response to LEPs distinguishes MCS from VS to a mildly important degree.
 - Low confidence in the evidence; 1 Class I study³² with decreased confidence in the evidence due to precision; LR+ 2.30, 95% CI 1.43-3.67

- ***Perturbational Complexity Index (PCI)***

- It is possible that a PCI > 0.31 distinguishes MCS from VS/UWS to a mildly important degree.
 - Low confidence in the evidence, 1 Class I study³⁰ with decreased confidence in the evidence due to precision; LR+ 3.375, 95% CI 1.87-6.09

Clinical Question 2

- What is the natural history of prolonged DoC?

Clinical Question 2: Natural History

Conclusions

- **Random-effects Meta-analyses**
- **Traumatic VS/UWS**
 - Combined results of 8 Class III studies (outcomes at 3 months,^{e4,e12,e20} 6 months,^{e4,e12,e20} 8 months,^{e5} 12 months,^{e4,e9,e10,e12,e20} and > 24 months^{e13} months postinjury) yielded single estimates.
 - See table 2 of the published systematic review summary article for meta-analyses data reflecting low confidence in the evidence for all 8 studies.
- **Nontraumatic VS/UWS**
 - Four Class III studies reported outcomes in patients with nontraumatic VS/UWS.^{e3,e5,e13,e14}
 - It is possible that 3-month survival is 80% (95% CI 67%-93%, $I^2 = 59$).
 - Low confidence in the evidence, 2 Class III studies^{e3,e13}
 - It is possible that 60% of patients (95% CI 45%-74%) will survive to 6-8 months.
 - Low confidence in the evidence, 2 Class III studies^{e3,e13}

Clinical Question 2: Natural History

Conclusions

- *Traumatic and Nontraumatic MCS*
 - No studies examined the natural history of patients in traumatic or nontraumatic MCS in a manner allowing outcome to be determined at specific times postinjury.
 - See table 2 of the published systematic review summary article for meta-analyses data reflecting low confidence in the evidence for all 8 studies.

Clinical Question 3

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

Clinical Question 3: Prognostic Assessment

Conclusions

- Four Class II studies^{e6,e8,e21,e22} examined the prognostic value of diagnoses of MCS vs VS/UWS.
- **Prolonged MCS**
 - A diagnosis of traumatic MCS, as opposed to traumatic VS/UWS, is probably associated with increased odds of better than severe disability at 12 months.
 - Moderate confidence in the evidence, 1 Class II study^{e22} with increased confidence in the evidence due to magnitude of effect
 - A diagnosis of MCS of mixed etiology is possibly associated with increased odds of improvement vs VS/UWS diagnosis (odds ratio [OR] 4.72, 95% CI 1.13–19.71, $I^2 = 66\%$).
 - Low confidence in the evidence, meta-analysis of 3 Class II studies^{e8,e21,e22} with insufficient precision to drive recommendations individually
- **Prolonged VS/UWS**
 - A VS/UWS diagnosis of mixed etiology—when condition already present for over a year—is possibly associated with increased odds of deterioration in functional status over subsequent years (OR 3.37, 95% CI 1.28–8.87).
 - Low confidence in the evidence, 1 Class II study^{e6}

Clinical Question 3: Prognostic Assessment

Conclusions

- One Class I and 4 Class II studies examined the prognostic value of traumatic vs nontraumatic injury in patients with prolonged DoC.^{e6,e8,e21-e23}
- **Traumatic DoC**
 - Traumatic MCS is probably associated with increased odds of better than severe disability at 12 months (OR 11.0, 95% CI 1.9-63.2).
 - Moderate confidence in the evidence, 1 Class II study^{e24} with increased confidence in the evidence due to magnitude of effect
- **Mixed Traumatic and Nontraumatic DoC**
 - Traumatic MCS and VS/UWS are probably associated with increased odds of improvement (defined generally due to differences in study design; OR of 9.41, 95% CI 2.03-43.53).
 - Moderate confidence in the evidence, 3 Class III studies,^{e8,e21,e24} 2 of which had sufficient precision on their own^{e21,e24} combined in a meta-analysis with overall increased confidence in the evidence due to magnitude of effect

Clinical Question 3: Prognostic Assessment

Conclusions

- *Prognostic Factors in DoC Subgroups by Etiology*
 - See table 3 of the systematic review summary article for prognostic factors associate with better or worse prognosis.
 - Nine studies^{e4,e10,e20,e22,e25-e29} (1 Class I, 7 Class II, 1 Class III) were identified looking at prognostic factors in patients with traumatic VS/UWS, although 3 of the Class II studies were based on largely the same subjects/study and thus were considered together.^{e10,e25,e30}
 - The measures of association are described in the full-length guideline.

Clinical Question 3: Prognostic Assessment

Conclusions

- *Prognostic Factors in Pediatric Populations*
 - Traumatic vs nontraumatic (anoxic) etiology of VS/UWS present for at least 30 days is possibly associated with increased odds of recovery at 3 to 12 months.
 - Low confidence in the evidence, 1 Class II study^{e36}
 - Traumatic etiology, compared with an anoxic injury, is probably also associated with a better quality outcome.
 - Moderate confidence in the evidence, 1 Class II study^{e36} with increased confidence due to magnitude of effect
 - In pediatric patients with a DoC for at least 90 days, a traumatic etiology, compared with an anoxic injury, is possibly associated with better cognitive and motor outcomes and increased odds of taking feedings orally.
 - Low confidence in the evidence, 1 Class II study^{e37}
 - Other prognostic features are described in table 3 of the systematic review summary article.

Clinical Question 4

- What treatments are effective for prolonged DoC?

Clinical Question 4: Treatments

Conclusion

- Two Class I therapeutic studies^{e38,e39} and 1 Class III therapeutic study^{e40} were identified.
- *Amantadine*
 - Amantadine probably hastens functional recovery in patients with MCS or VS/UWS secondary to severe traumatic brain injury over 4 weeks of treatment and appears safe in this population.
 - Moderate confidence in the evidence, 1 Class I study^{e38}
 - There is insufficient evidence to support or refute continuation of benefit once amantadine is discontinued.
 - Very low confidence in the evidence, 1 Class I study^{e38} with insufficient precision

Clinical Question 4: Therapeutic Intervention

Conclusion

- *Tilt Table Treatment*

- In patients with VS/UWS of mixed etiologies, conventional tilt table treatment is probably superior to tilt table treatment incorporating an integrated stepping device for improving level of arousal.
 - Moderate confidence in the evidence based on 1 Class I study^{e39}
- The benefit of tilt table treatment vs placebo/nontreatment is not established.
 - No identified studies

Clinical Context

• Gaps in Knowledge

- Some consistent weaknesses in study methodology were observed across studies.
 - Most prevalent was small sample size.
 - Limited study precision and generalizability
- The a priori inclusion criteria constrained the number of available studies.
 - Including only those studies investigating individuals who were at least 28 days postinjury disqualified many studies.
 - Conducted in the acute care setting
 - Combined, or did not specify, the number of individuals above and below this threshold
- Some well-designed studies where most individuals met criterion were considered as strong related evidence in some recommendation rationales.

Clinical Context

- **Diagnostic Assessment**

- Biggest challenge to validating more precise diagnostic approaches is lack of an established reference (gold) standard with adequate sensitivity and specificity.
 - The most commonly used, team consensus-based diagnosis, associated with a 30%-40% error rate¹³⁻¹⁵
 - Not known whether disagreement between the reference standard and a novel assessment measure reflects (1) false-positive or false-negative error on the part of the novel measure or (2) evidence that the novel measure has outperformed the reference standard
- Infrequent use of masking procedures, essential to protect against examiner bias, is particularly important when the assessment approach relies on nonobjective measures.

Clinical Context

- Natural History

- Investigation of the natural history of recovery from severe brain injury requires a systematic approach to tracking selected milestones.
 - Many studies failed to report or control for the length of time from injury and instead anchored follow-up to date of inpatient rehabilitation admission.
 - Studies often failed to stratify or subanalyze individuals by diagnostic subtype and etiology, obscuring recovery trajectory.
 - A further limitation is the fact that most natural history studies enroll individuals at specialty rehabilitation centers, affecting generalizability.
- Relatively few natural history and prognostic studies reported long-term functional outcomes.
 - Often outcome assessment focused exclusively on recovery of consciousness or emergence from MCS or both, without attention to the corresponding disability level.
 - Studies that tracked functional outcome beyond 1 year suggest up to 1 in 5 patients with prolonged DoC eventually regain independence at home.^{e41,e42}
- DoC outcome research will be of greater relevance to clinicians, patients, and families by ensuring that results address the degree of functional improvement attained.

Clinical Context

- **Prognostic Assessment**

- Most studies investigating the predictive utility of patient and injury characteristics were conducted retrospectively.
 - Led to some of the same limitations noted in the natural history studies
- Inclusion criteria did not address specific clinical features known to be linked to outcome, and thus within-sample variability tended to be high along these dimensions.
 - Led to wide CIs and imprecise outcome projection
- Often, risk factors and outcomes were not assessed independently
 - Raised possibility that factors believed to affect prognosis may have inappropriately influenced clinical decisions and contributed to unfavorable outcomes.

Clinical Context

- **Therapeutic Intervention**

- Most treatment studies were excluded because the intervention was studied during the acute phase of recovery, there was no control group, or the study was not methodologically sound.
 - DoC treatment studies face challenges not encountered in clinical trials conducted in other populations (e.g., fewer admissions to inpatient rehabilitation facilities and shorter lengths of stay due to changes in insurance reimbursement trends).
 - The typical length of inpatient rehabilitation in many academic medical centers has fallen below 20 days.
- Family members often are reluctant to enroll patients with prolonged DoC in a placebo-controlled trial because of the 50% likelihood of assignment to the placebo arm.

Practice Recommendations

- **Recommendation 1 Rationale**

- Our systematic review highlights the complexities of caring for patients with prolonged DoC (i.e., ≥ 28 days) at every stage.
 - May be misdiagnosed due to confounding neurologic deficits² or inexperience in examining patients for subtle signs of consciousness³
 - Accurate diagnosis important to educate families about patients' level of consciousness and function, inform prognostic counseling, and guide treatment decisions
- Knowledge gaps often lead to overestimation or underestimation of prognosis by nonspecialists.⁴
- Patients with prolonged DoC frequently experience significant medical complications that can slow recovery and interfere with treatment interventions.⁵
- 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 who are knowledgeable about the risks associated with DoCs and are capable of initiating timely treatment.
- This is supported by findings from a large retrospective trauma registry which found that cumulative mortality at 3 years postdischarge is significantly lower for patients discharged to home or inpatient rehabilitation facilities than those discharged to skilled nursing facilities, even after adjusting for covariates.⁶
- Care for patients with prolonged DoC may benefit from a team of multidisciplinary rehabilitation specialists, including neurologists, psychologists, neuropsychologists, physiatrists, physical therapists, occupational therapists, speech pathologists, nurses, nutritionists, internists, and social workers.

Practice Recommendations

• Recommendation 2 Rationale

- The range of physical and cognitive impairments experienced by individuals with severe DoC complicate diagnostic accuracy and make it difficult to distinguish behaviors that are indicative of conscious awareness from those that are random and nonpurposeful.
 - Interpretation of inconsistent behaviors or simple motor responses are particularly challenging.
 - Fluctuations in arousal and response to command further confound the reliability of clinical assessment.^{7,8}
 - Underlying central and peripheral impairments, such as aphasia, neuromuscular abnormalities and sensory deficits, may also mask conscious awareness.⁹⁻¹¹
- Clinician reliance on nonstandardized procedures, even when the examination is performed by experienced clinicians,^{2,12,13} contributes to diagnostic error, which consistently hovers around 40%.
 - Diagnostic error includes misdiagnosing the locked-in syndrome for VS/UWS and MCS.^{14,15}
- Accurate diagnosis of the level of consciousness has implications for prognosis and management.
- *For additional rationale content, see the published full-length guideline.*

Practice Recommendations

Recommendation Statements 1, 2a–2d: Overall Care and Diagnosis for Adults

- 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**).
- 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).
- 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).
- 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).
- 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).

Practice Recommendations

Recommendation Statements 2e, 2f: Overall Care and Diagnosis for Adults

- 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).
- 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.

Practice Recommendations

- **Recommendation 3 Rationale**

- In patients with severe traumatic brain injury (TBI), many of whom have a DoC, 1 study found that hospital mortality was 32%, with 70% of those deaths associated with the withdrawal of life-sustaining therapy.⁴
 - Withdrawal of life-sustaining therapy was more closely associated with the facility where care was provided than with baseline characteristics, including age, sex, pupillary reactivity, and Glasgow Coma Scale motor score.⁴
- While withdrawal of life-sustaining therapy was high, this systematic review identified that individuals with a DoC lasting longer than 1 month postinjury may still attain functionally significant recovery after 1 year postinjury.
 - Additional research shows that patients with prolonged DoC can achieve at least some degree of functional independence during long-term follow-up.
 - For example, one study found that approximately 20% of patients with a traumatic VS/UWS DoC admitted to inpatient rehabilitation were judged to be functionally independent and capable of returning to employment at 1, 2, or 5 years.²⁸
 - Another longitudinal study including patients with traumatic and nontraumatic DoC reported that almost half of the sample recovered to at least daytime independence at home and 22% returned to school or work.²⁹
 - While these studies may not be fully generalizable, they suggest the potential for recovery in this population, which has implications for prognostic discussions.

Practice Recommendations

• Recommendation 4 Rationale

- The natural history of DoC is not well defined, particularly for populations with nontraumatic brain injury, and diagnosis and prognosis can be challenging.
- Individuals with DoC can fluctuate between different diagnostic categories.
- Fluctuation is particularly common early in the course of recovery,³⁰ and one study suggests a 30% probability of observing behaviors suggestive of MCS in patients diagnosed with VS/UWS when assessments are conducted in the morning.⁷
- Patients with VS may also emerge to MCS over time.
- MCS is probably associated with a better prognosis than VS.
- Serial examinations, already suggested to improve diagnostic accuracy, may also aid prognosis in view of the relationship between diagnosis and prognosis.

Practice Recommendations

• Recommendation 5 Rationale

- In patients diagnosed with prolonged traumatic VS/UWS, Disability Rating Scale (DRS) scores < 26 at 2-3 months postinjury, a detectable P300 at 2-3 months postinjury, a reactive EEG at 2-3 months postinjury, and higher-level activation of the auditory association cortex using blood oxygen level dependent (BOLD) fMRI in response to a familiar voice speaking the patient's name probably have prognostic utility, suggesting an increased chance of recovering consciousness within 12 months.
- A normal SPECT scan at 1-2 months postinjury, lower DRS scores in general 2-3 months postinjury, and a detectable P300 2-3 months postinjury after controlling for DRS and EEG reactivity are possibly associated with either an increased likelihood of recovery of consciousness or a more favorable outcome, while MRI imaging performed 6-8 weeks postinjury showing corpus callosal lesions, dorsolateral upper brainstem injury, or corona radiata injury are possibly associated with a worse prognosis at 12 months.

Practice Recommendations

- **Recommendation 6 Rationale**

- In patients diagnosed with nontraumatic postanoxic VS/UWS, it is highly probable that Coma Recovery Scale-Revised (CRS-R) scores of ≥ 6 obtained more than 1 month after onset and the presence of somatosensory evoked potentials from bilateral median nerve stimulation each have prognostic utility as independent predictors of recovery, suggesting an increased likelihood of recovery of responsiveness by 24 months postinjury.

Practice Recommendations

- **Recommendation 7 Rationale**

- The 1994 AAN Multi-Society Task Force defined VS as “permanent” 3 months after a nontraumatic injury leading to VS and 12 months following a traumatic injury, acknowledging that unexpected recoveries will occur after these times but that these cases will be rare and typically associated with severe disability.³¹
 - A reanalysis of the Task Force data concluded that the estimated rates of late recovery for traumatic and nontraumatic VS were unreliable due to inconsistent follow-up, unreliable reporting, and questionable diagnostic accuracy.³²
 - Relying only on the portion of the Task Force dataset that was extracted from the Traumatic Coma Data Bank,³³ 6 patients (14%) recovered consciousness between 1 and 3 years postinjury. This recovery rate is substantially higher than the 1.6% reported in the Task Force Report and raised questions about the appropriateness of the term “permanent VS.”
- In the current systematic review, no study evaluated the prognosis of patients with traumatic VS/UWS after 12 months of injury.
 - One Class II study mixing patients with traumatic and nontraumatic VS/UWS found that none of these patients in VS/UWS 12 months after onset improved when assessed at 2, 3, 4, and 5 years postinjury, but due to the small sample size, confidence intervals for the possibility of improving were wide (0%, 95% CI 0%-24%).³⁴

Practice Recommendations

• Recommendation 7 Rationale

- Recent studies suggest that some patients with prolonged nontraumatic VS/UWS may experience ongoing recovery after 3 months.
- Meta-analyses performed in this systematic review found it is possible that 17% (95% CI 5%-30%) will recover consciousness at 6 months. After 6 months, it is possible that an estimated 7.5% (95% CI 0%-24%) may recover consciousness.
- In one study of prolonged anoxic vegetative state included in the systematic review, of the 9 of 43 recovering responsiveness, 2 recovered between 3-6 months, 3 recovered at 6-12 months, and 4 recovered at 12-24 months.
 - Of the 2 individuals emerging from MCS, 1 patient recovered consciousness at 16 months and emerged from MCS at 18 months and the other recovered consciousness at 22 months and emerged from MCS at 25 months; both remained severely disabled.
 - Of 41 patients who remained in VS/UWS at 6 months, 7 additional patients recovered consciousness before 24 months (17%, 95% CI 9%-31%).³⁵
- The natural history of nontraumatic VS/UWS is likely tied to the underlying etiology, with nontraumatic VS/UWS related to a specific insult (e.g., anoxic injury, ischemia) different from that relating to ongoing neurodegeneration.

Practice Recommendations

• Recommendation 7 Rationale

- Additional evidence suggests that late transition to MCS from VS/UWS may occur in as many as 20% of patients who meet permanence criteria.
 - One study followed 50 patients who remained unconscious for a mean of 11.1 (\pm 4.8) months after traumatic or nontraumatic brain injury and reported that 10 patients (7 traumatic, 3 nontraumatic) recovered consciousness between 14 and 28 months postonset.³⁶
 - A second study followed 108 patients with TBI across a 5-year interval, all of whom failed to recover command-following during the course of inpatient rehabilitation. Among the 17 patients who were still unable to follow commands at 12 months postonset, 8 (47.0%) regained this ability between 1 and 5 years postinjury.²⁸
 - Although the majority of patients who remain in VS/UWS across the first 3 (after nontraumatic) and 12 months (after traumatic) postinjury will remain in this condition permanently, a substantial minority will recover consciousness beyond this time frame.
 - While most of these patients will be left with severe disability, functional outcome ratings indicate that some will regain the ability to communicate reliably, perform self-care activities, and interact socially.³⁷

Practice Recommendations

• Recommendation 7 Rationale

- In view of these findings, continued use of the term “permanent VS” is not justified.
 - Use of this term implies “irreversibility” which is not supported by the current research and which has implications for family counseling, decision-making, and the ethics of the field.
- The guideline panel suggests that the term “permanent VS” be replaced by the term “chronic VS” to indicate the stability of the condition (in keeping with other diseases that have a chronic phase).
 - This should be accompanied by a description of the current duration of the VS/UWS, as evidence supports a decreasing likelihood of recovery with longer duration of unresponsiveness.
 - Because most patients with late recovery of consciousness will remain fully or partially dependent upon others for activities of daily living, prognostic counseling should emphasize the need for long-term care and specify the type of supportive care required.

Practice Recommendations

Recommendation Statements 3–7: Prognosis for Adults

- 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**).
- Clinicians caring for patients with prolonged DoC should perform serial standardized behavioral evaluations to identify trends in the trajectory of recovery that are important for establishing prognosis (**Level B**).
- Posttraumatic VS/UWS: Clinicians should perform the DRS at 2–3 months postinjury (**Level B**) and may assess for the presence of P300 at 2–3 months postinjury (**Level C** based on feasibility) or assess EEG reactivity at 2–3 months postinjury (**Level C** based on feasibility) to assist in prognostication regarding 12-month recovery of consciousness for patients in traumatic VS/UWS. Clinicians should perform MRI 6–8 weeks postinjury to assess for corpus callosal lesions, dorsolateral upper brainstem injury, or corona radiata injury in order to assist in prognostication regarding remaining in PVS at 12 months for patients in traumatic VS/UWS (**Level B**). Clinicians should perform a SPECT scan 1–2 months postinjury to assist in prognostication regarding 12-month recovery of consciousness and degree of disability/recovery for patients in traumatic VS/UWS (**Level B**). Clinicians may assess for the presence of higher level activation of the auditory association cortex using BOLD fMRI in response to a familiar voice patient’s name to assist in prognostication regarding 12-month (postscan) recovery of consciousness for patients in traumatic VS/UWS 1–60 months postinjury (**Level C** based on feasibility, cost).
- Nontraumatic, postanoxic VS/UWS: Clinicians should perform the CRS-R (**Level B**) and may assess somatosensory evoked potentials (**Level C** based on feasibility) to assist in prognostication regarding recovery of consciousness at 24 months for patients in nontraumatic postanoxic VS/UWS.
- 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**).

Practice Recommendations

• Recommendation 8 Rationale

- Systematic review evidence showed that in patients with prolonged DoC, those diagnosed with MCS within the first 5 months of injury have a more favorable long-term prognosis for functional recovery than those diagnosed with VS/UWS.
 - Long-term prognosis is also more favorable in patients in MCS who have sustained traumatic vs nontraumatic brain injury.³⁸
 - The evidence reviewed does not clearly support or refute age and time postinjury as prognostic features.
- As described in the rationale for recommendation 3 (see earlier slide), evidence from the systematic review identified that individuals with a DoC at 1 month postinjury may still attain functionally significant recovery after 1 year postinjury, with additional longitudinal studies showing that approximately 20% of patients recover to the level where they could return to work or school.^{28,29}

Practice Recommendations

- **Recommendation 9 Rationale**

- Patients with prolonged DoC may have a prolonged recovery over months to years, and many will remain severely disabled.
- Employment and personal finances in the short term and the long term will be significantly impacted, and these effects will have implications for family members.
- Patients and families benefit from planning in advance for an expected prolonged recovery.

- **Recommendation 10 Rationale**

- See rationale for recommendation 7.

Practice Recommendations

Recommendation Statements 8–10: Counseling on Prognosis for Adults

- 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).
- In patients with a prolonged DoC, once a prognosis has been established that indicates a likelihood of severe long-term disability, clinicians must counsel family members to seek assistance in establishing goals of care and completing state-specific forms regarding medical decision-making (e.g., medical orders for life-sustaining treatment [MOLST] forms), if not already available, applying for disability benefits, and starting estate, caregiver, and long-term care planning (**Level A**).
- When patients enter the chronic phase of VS/UWS (i.e., 3 months after non-TBI and 12 months after TBI), prognostic counseling should be provided that emphasizes the likelihood of permanent severe disability and the need for long-term assistive care (**Level B**).

Practice Recommendations

- **Recommendation 11 Rationale**

- Preexpressed wishes of patients with prolonged DoC and values of families of persons with prolonged DoC can be highly variable.
 - Values may also change over the course of illness.
 - Personal values should be identified early and need to be reassessed over time when making decisions regarding care for individuals with prolonged DoC.

Practice Recommendations

• Recommendation 12 Rationale

- Complication rates are high in patients with prolonged DoC and negatively affect morbidity and mortality.^{5,39,40,e1}
- It is important that clinicians remain vigilant to medical complications in the short term to facilitate their early identification and to help optimize long-term outcomes.
- The most common complications in patients with prolonged DoC include agitation/aggression, hypertonia, sleep disturbance, and urinary tract infections.³⁷
- Other, more severe complications, such as hydrocephalus, pneumonia, and paroxysmal sympathetic hyperactivity, can disrupt rehabilitation efforts, as they often require rehospitalization.³⁷
- Strategies for early detection and rapid management of complications include daily physician rounds, 24-hour specialty physician coverage, on-site availability of diagnostic resources, and timely access to specialty consultations.³⁷

Practice Recommendations

• Recommendation 13 Rationale

- The potential to experience pain and suffering is an issue frequently raised with respect to treatment, ethical, and legal questions in individuals with DoC.
 - Some studies using functional imaging indicate that brain activation in networks supporting pain perception is lower in patients diagnosed with VS compared with those in MCS and conscious controls, suggesting that patients in VS lack capacity for full pain awareness.^{e2,e3}
 - Other studies suggest that the relationship between level of consciousness and pain perception is unclear.^{e4,e5}
- Accurate assessment of pain and suffering in individuals with DoC is limited by challenges in accurately diagnosing pain due to the level of consciousness and conflicting evidence regarding the potential of patients in VS or MCS to experience pain and suffering.
- Clinicians should be cautious in making definitive conclusions about pain and suffering in individuals with DoC.

Practice Recommendations

• Recommendation 14 Rationale

- Amantadine (100-200 mg twice daily), when administered over a period of 4 weeks in patients between 16 and 65 years old with traumatic DoC who are between 4 and 16 weeks of injury, probably hastens functional recovery in the early stages.
- Faster recovery reduces the burden of disability, lessens health care costs, and minimizes psychosocial stressors in patients and caregivers.

Practice Recommendations

• Recommendation 15 Rationale

- Most therapies proposed for treating patients with DoC have insufficient evidence to support or refute their use, and many have associated risks.
- Families may pursue these treatments in the absence of evidence because they are desperate for ways to help their loved one and interventions supported by high-quality evidence are sparse.
- Counseling families about treatment effectiveness is complicated by the difficulties inherent in determining whether improvements observed early in the course of recovery are related to interventions or due to spontaneous recovery.

Practice Recommendations

Recommendation Statements 11–15: Care and Treatment of Adults

- Clinicians must identify patient and family preferences early and throughout provision of care to help guide the decision-making process for persons with prolonged DoC (**Level A**).
- 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**).
- Clinicians should assess individuals with a DoC for evidence of pain or suffering and should treat when there is reasonable cause to suspect that the patient is experiencing pain (Level B), regardless of level of consciousness. Clinicians should counsel families that there is uncertainty regarding the degree of pain and suffering that may be experienced by patients with a DoC (**Level B**).
- Clinicians caring for patients with traumatic VS/UWS or MCS who are between 4 and 16 weeks postinjury 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**).
- 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**). When discussing nonvalidated treatments, clinicians should provide evidence-based information regarding the projected benefits and risks of a particular treatment and the level of uncertainty associated with the proposed intervention, keeping in mind that families and caregivers are often in distress and vulnerable (**Level B**). 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**).

Practice Recommendations

- **Recommendation 16 Rationale**

- No evidence was identified regarding the diagnosis of children with prolonged DoC.
- In the absence of pediatric-specific evidence, it is reasonable to apply the diagnostic recommendations for adult populations that address the treatment of confounding conditions to improve diagnosis, the importance of increasing arousal prior to diagnostic assessments, using valid and reliable standardized behavioral assessments, and conducting serial assessments to children with DoC.

- **Recommendation 17 Rationale**

- The natural history of DoC in children is not well defined.
 - In children with a prolonged DoC, traumatic etiology is possibly associated with a better chance of recovery, as is the absence of posttraumatic autonomic dysfunction.
 - Posttraumatic hyperthermia may be associated with a worse outcome.
 - No other evidence was identified.

Practice Recommendations

- **Recommendation 18 Rationale**

- No identified therapeutic studies enrolled pediatric populations. The only therapeutic intervention shown to have efficacy in adults (16-65 years) is amantadine.
- A retrospective case-controlled study of amantadine use in patients with TBI reported that 9% of children taking this treatment had side effects, but methodologic concerns limit therapeutic conclusions from this study.

Practice Recommendations

Recommendation Statements 16–18: Care of Children

- Clinicians should treat confounding conditions, increase arousal prior to diagnostic assessments, use valid and reliable standardized behavioral assessments (particularly those targeting pediatric populations), and conduct serial assessments to improve diagnostic accuracy in children with prolonged DoC (**Level B**).
- Clinicians should counsel families that the natural history and prognosis of children with prolonged DoC is not well-defined and that there are no current evaluations established to improve prognostic accuracy in this population (**Level B**).
- Clinicians should counsel families that there are no established therapies for children with a prolonged DoC (**Level B**).

Suggestions for Future Research

- This practice guideline and accompanying systematic review highlight the methodologic complexities and limitations associated with clinical management of patients with prolonged DoC.
 - In most of the areas reviewed, the degree to which the current findings can be applied to clinical practice remains uncertain.
 - The results have identified methodologic shortcomings that cut across most studies, as well as others that are specific to a particular type of study.
- ***For the full set of future research suggestions, see the published full-length guideline.***

References

References cited here can be found in the recommendations summary article and systematic review summary article. To locate these materials, please visit [AAN.com/guidelines](https://www.aan.com/guidelines).

Access Guideline and Summary Tools

- To access the complete guideline and related summary tools, visit [AAN.com/guidelines](https://www.aan.com/guidelines).
 - Summary recommendations and systematic review articles
 - Complete guideline article (available as a data supplement to the recommendations summary article)
 - Summary for clinicians and summary for patients/families

Questions?