SPECIAL ARTICLE

Comprehensive systematic review update 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

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Abstract

Objective

To update the 1995 American Academy of Neurology (AAN) practice parameter on persistent vegetative state and the 2002 case definition for the minimally conscious state (MCS) by reviewing the literature on the diagnosis, natural history, prognosis, and treatment of disorders of consciousness lasting at least 28 days.

Methods

Articles were classified per the AAN evidence-based classification system. Evidence synthesis occurred through a modified Grading of Recommendations Assessment, Development and Evaluation process. Recommendations were based on evidence, related evidence, care principles, and inferences according to the AAN 2011 process manual, as amended.

Results

No diagnostic assessment procedure had moderate or strong evidence for use. It is possible that a positive EMG response to command, EEG reactivity to sensory stimuli, laser-evoked potentials, and the Perturbational Complexity Index can distinguish MCS from vegetative state/unresponsive wakefulness syndrome (VS/UWS). The natural history of recovery from prolonged VS/UWS is better in traumatic than nontraumatic cases. MCS is generally associated with a better prognosis than VS (conclusions of low to moderate confidence in adult populations), and traumatic injury is generally associated with a better prognosis than nontraumatic injury (conclusions of low to moderate confidence in adult and pediatric populations). Findings concerning other prognostic features are stratified by etiology of injury (traumatic vs nontraumatic) and diagnosis (VS/UWS vs MCS) with low to moderate degrees of confidence. Therapeutic evidence is sparse. Amantadine probably hastens functional recovery in patients with MCS or VS/UWS secondary to severe traumatic brain injury over 4 weeks of treatment. Recommendations are presented separately.

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Glossary

AAN = American Academy of Neurology; **CI** = confidence interval; **DoC** = disorders of consciousness; **eMCS** = emergence from minimally conscious state; **LEP** = laser-evoked potential; **LR** = likelihood ratio; **MCS** = minimally conscious state; **MSTF** = Multi-Society Task Force; **OR** = odds ratio; **PVS** = persistent vegetative state; **UWS** = unresponsive wakefulness syndrome; **VS** = vegetative state.

In simplest terms, consciousness is defined as the state of awareness of the self and environment.[1] Conscious behavior requires adequate arousal (i.e., wakefulness) and awareness of content (i.e., sensory, cognitive, and affective experience). Severe acquired brain injury (ABI) is a catastrophic event that disrupts the brain's arousal and awareness systems, which are mediated by the brainstem and cortex, respectively. The most severe injuries result in prolonged (i.e., lasting at least 28 days) disorders of consciousness (DoC), including the vegetative state (VS)[2] and the minimally conscious state (MCS).[3] VS is also referred to as postcoma unawareness[4] or unresponsive wakefulness syndrome (UWS).[5] In this guideline, the term UWS is used synonymously with VS. While this term has no special merit or mandate for use in clinical practice, it is included here because of its wide acceptance in Europe. Table e-1 (links.lww.com/WNL/A611) provides the definitions for VS and MCS and other key terms pertinent to DoC.

The cost of lifetime care for persons with prolonged DoC can exceed $1,000,000.[6] Despite the enormity of the problem, few practice guidelines are available. In 1995, the American Academy of Neurology (AAN) published diagnostic and prognostic guidelines for persistent VS (PVS)[7] 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] Both reports focused on diagnosis, as data addressing prognosis and treatment were sparse.

Based on available epidemiologic data,[8] the annual US incidence of VS is approximately 4,200 persons. The incidence of MCS is unknown largely because it has no diagnostic code in the International Classification of Diseases classification system. Prevalence figures for VS/UWS and MCS in the United States are 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. Prevalence estimates range from 5,000 to 42,000 persons for VS/UWS[9–11] and 112,000 to 280,000 persons for MCS using a proxy definition.[12]

Published estimates of misdiagnosis among patients with DoC consistently approximate 40% in both US and European studies.[13–15] In the most recent study,[13] 41% of patients with a clinical diagnosis of VS/UWS based on team consensus (n = 44) were actually in MCS when reevaluated by the investigators using a standardized neurobehavioral scale. In addition, 89% of those with an uncertain diagnosis (n = 18) were found to have clear signs of consciousness on standardized examination. Findings from the other 2 studies[14,15] were in the same direction. Underlying visual or motor impairments interfering with detection of command-following and failure to detect visual pursuit are frequent causes of failure to recognize MCS. The rate of diagnostic error underscores the need for more refined evaluation methods. This concern extends to the criteria for emergence from MCS (eMCS), as some investigators suggest that the existing criteria lead to overdiagnosis of this condition.[16]

Now is an opportune time to reevaluate current diagnostic approaches. Apart from the extensive list of specialized neurobehavioral assessment instruments that have been released since the MSTF and Aspen Neurobehavioral Workgroup reports were published,[2,17] a growing body of research suggests that functional neuroimaging techniques, such as fMRI and PET, may be able to detect suggestions of conscious awareness in the absence of bedside evidence.[18–21]

Natural history studies of patients with prolonged DoC now include outcomes extending beyond 1 year. This provides an opportunity to reassess the 1994 MSTF introduction of the term permanent VS (table e-1, links.lww.com/WNL/A611), which is questioned based on the methodology used to calculate the incidence of recovery of consciousness beyond 12 months[22] and the total number of individuals available for follow-up after 12 months (i.e., 30).[23] Increasingly, publications are also available for DoC prognosis and treatment, with recent multicenter randomized clinical trials available to determine the effectiveness of specific interventions for patients with prolonged DoC.

The purpose of this systematic review and accompanying guideline is to update the 1995 AAN PVS guideline[7] and the 2002 MCS case definition.[3] This article summarizes the systematic review findings and conclusions. The guideline recommendations are published separately.[24] Full text of the systematic review and guideline, including appendices e-1 to e-9, is available as a data supplement at links.lww.com/WNL/A610. Tables e-1 to e-3 and references e1 through e42, cited here, are also available at links.lww.com/WNL/A612.

This review aimed to answer 10 clinical questions (table e-2, links.lww.com/WNL/A611), which can be summarized in 4

Supplemental Data

Full text of guideline at:
NPub.org/m5ii8i

overarching questions concerning patients with traumatic and nontraumatic DoC: (1) What procedures accurately diagnose prolonged DoC, where prolonged DoC is defined as lasting at least 28 days? (2) What is the natural history of prolonged DoC? (3) What factors or procedures help to predict outcome in prolonged DoC? (4) What treatments are effective for prolonged DoC?

Description of the analytic process

This systematic review and accompanying practice guideline were developed in accordance with the process described in the 2011 AAN Clinical Practice Guideline Process Manual, as amended.[25] The full guideline provides a description of the exact methodology followed, including the processes of convening the author panel, performing the literature search, and reviewing the evidence and application of a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.[26] Recommendations were based not only on the evidence in the systematic review, but also on strong related evidence, established principles of care, and inferences. The level of obligation for each recommendation was based on the strength of these premises and the risk–benefit ratio of following the recommendation, with adjustments based on importance of outcomes, variation in patient preferences, feasibility/availability, and patient costs. Consensus was determined by a modified Delphi voting process in accordance with prespecified rules.[25]

Inclusion criteria relevant for all questions were (1) population had a DoC for at least 28 days and (2) the study enrolled at least 20 patients with a prolonged DoC. The 28-day cutoff was employed to ensure that patients in coma were excluded, as good outcome is not uncommon following transient coma, unlike prolonged VS/UWS and MCS. Articles were accepted only if the entire participant population met the criterion of having a DoC for at least 28 days or if the article presented data for this cohort separately. This approach was determined a priori and resulted in the exclusion of some high-quality studies. This is discussed further in the Putting the Evidence in a Clinical Context section.

Analysis of evidence

Diagnostic assessment

For the diagnostic question, the guideline panel considered patients with traumatic or nontraumatic VS/UWS or MCS at least 28 days postinjury and asked if any diagnostic assessment procedures accurately detect behavioral signs of consciousness or differentiate specific DoC compared with standardized behavioral assessment. Readers are referred to a previously published systematic review completed by the American Congress of Rehabilitation Medicine Disorders of Consciousness Task Force that provides evidence-based recommendations for clinical use of standardized behavioral assessment methods (work not repeated in this project).[17] Study results were assessed using likelihood ratios (LRs), which are described in the full-length guideline.

Eight diagnostic articles were Class I for at least some procedures,[27–34] 4 articles were Class II,[29,35–37] and 4 articles were Class III[38–40,e1] (links.lww.com/WNL/A612). No diagnostic assessment procedure had moderate or strong evidence for use (table 1). For distinguishing VS and MCS, there was insufficient evidence to support or refute the use of EMG activity to command after adjusting for involuntary movements,[27] normal or mildly abnormal background on EEG,[29,31] the combination of a low-voltage background EEG pattern and lack of EEG reactivity,[31] specific entropy measures,[38] the absence of Aδ-fiber laser-evoked potential (LEP) N2P2 or C-fiber LEP N2P2 components in response to LEPs,[e2] evidence of exogenous or endogenous attention as assessed by the P3a and P3b components of P300 in response to word stimuli,[35] a nasal cannula "sniff controller,"[28] command-following on an fMRI motor imagery task,[29] use of an fMRI incorrect-minus-correct activation protocol,[36] resting-state MRI,[37] structural MRI,[37] or fluorodeoxyglucose-PET,[37] often due to limited precision. It is possible that fMRI using a word-counting task is not helpful in distinguishing between MCS and VS (low confidence in the evidence, 1 Class I study,[33] with the LR+ suggesting no change in the probability of MCS with testing and confidence intervals (CIs) suggesting values of slight importance at most; LR+ 1.00, 95% CI 0.33–2.99). Results for this study were affected by the fact that 3 of 8 patients diagnosed with VS/UWS based on the absence of command following on the CRS-R had the suggestion of fMRI activation with the task (37.5%, 95% CI 13.7%–69.4%), the implications of which are uncertain.

Natural history

Eighteen articles[e3–e20] (links.lww.com/WNL/A612) met inclusion criteria for the natural history question. Results were analyzed separately by DoC diagnosis and etiology; studies only reporting mixed etiology populations are described in the full-length guideline. 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.

Natural history of patients with traumatic VS/UWS

Eight Class III studies were identified, reporting outcomes at 3 months[e4,e12,e20] (links.lww.com/WNL/A612), 6 months,[e4,e12,e20] 8 months,[e5] 12 months,[e4,e9,e10,e12,e20] and >24 months[e13] postinjury. Most studies were Class III due to recruitment from specialty rehabilitation centers, thus limiting generalizability. Results were combined in random-effects meta-analyses to result in single estimates (table 2), each reflecting low confidence in the evidence. Comprehensive results are presented in the full-length guideline.

Natural history of patients with nontraumatic VS/UWS

Four Class III studies reported outcomes in patients with nontraumatic VS/UWS[e3,e5,e13,e14] (links.lww.com/WNL/A612). Six- and 24-month recovery estimates are presented in table 2. It is possible that 3-month survival for patients with

Table 1 Conclusions regarding diagnostic assessments with evidence for use in prolonged disorders of consciousness (DoC)

Diagnostic assessment	Conclusion
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 (LR+ 23.0, 95% CI 1.5–355.6) (low confidence in the evidence, 1 Class I study[34] 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 study[31] with decreased confidence in the evidence due to precision; LR+ 2.00, 95% CI 1.43–2.80).
Evoked potentials	It is possible that the presence of Aδ-LEP N2P2 and C-LEP N2P2 components in response to LEPs distinguishes MCS from VS to a mildly important degree (low confidence in the evidence; 1 Class I study[32] with decreased confidence in the evidence due to precision; LR+ 2.30, 95% CI 1.43–3.67).
PCI score	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 study[30] with decreased confidence in the evidence due to precision; LR+ 3.375, 95% CI 1.87–6.09).

Abbreviations: CI = confidence interval; LEP = laser-evoked potential; LR+ = positive likelihood ratio; MCS = minimally conscious state; PCI = Perturbational Complexity Index; VS/UWS = vegetative state/unresponsive wakefulness syndrome.

nontraumatic VS/UWS 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 with nontraumatic VS/UWS (95% CI 45%–74%) will survive to 6–8 months (low confidence in the evidence, 2 Class III studies).[e3,e13]

Prognostic assessment

For the prognostic question, the guideline panel first evaluated the prognostic relevance of DoC diagnosis (VS/UWS vs MCS) and of mechanism of injury. Then, the panel separately considered prognostic factors in patients with traumatic or nontraumatic VS/UWS or MCS at least 28 days postinjury because this information has the most clinical relevance. Prognostic factors for which there was insufficient evidence are described only in the full-length guideline.

Prognostic factors in adult populations

Four Class II studies[e6,e8,e21,e22] (links.lww.com/WNL/A612) examined the prognostic value of diagnoses of MCS vs VS/UWS. In prolonged DoC of traumatic origin, a diagnosis of MCS, as opposed to 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). In patients with prolonged DoC of mixed etiology, a diagnosis of MCS is possibly associated with increased odds of improvement vs VS/UWS (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). In patients with a prolonged DoC of mixed etiology already present for over a year, a diagnosis of VS/UWS 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]

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] (links.lww.com/WNL/A612). In patients with prolonged MCS, a traumatic etiology 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). In mixed populations including patients with MCS and VS/UWS, traumatic DoC is probably associated with increased odds of improvement (defined generally due to differences in study design; OR 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).

Table 2 Cumulative recovery of consciousness in disorders of consciousness (DoC) lasting ≥28 days

Type of DoC	3 months	6 months	12 months	24 months
Posttraumatic VS/UWS	38% (29%–47%)	67% (58%–76%)	78% (69%–86%)	
Nontraumatic VS/UWS		17% (5%–30%)[a]		7.5% (0%–24%)[b]

Abbreviation: VS/UWS = vegetative state/unresponsive wakefulness syndrome.
Values are % (95% CI).
[a] This meta-analysis included studies of patients 6–8 months postinsult.
[b] These estimates are for patients still in a DoC at 6 months and reflects a meta-analysis of 2 studies[e3,e13] (links.lww.com/WNL/A612) published 20 years apart (1993 and 2013), with high heterogeneity in the meta-analysis.

Table 3 Prognostic features in disorders of consciousness (DoC) ≥28 days

	Prognostic factors associated with better prognosis		Prognostic factors associated with worse prognosis	
Type of DoC	**Moderate confidence**	**Low confidence**	**Moderate confidence**	**Low confidence**
Adult traumatic VS/UWS	Higher-level activation of the associated auditory cortex using BOLD fMRI in response to a familiar voice speaking the patient's name	Normal SPECT scan 1–2 months postinjury	Hydrocephalus in the late phase	Corpus callosum lesions, dorsolateral upper brainstem injury, or corona radiata injury on MRI performed 6–8 weeks postinjury
	DRS scores of <26, 2–3 months postinjury	Lower scores on the DRS in general 2–3 months postinjury		Fever of central origin in the acute phase
	Detectable P300 at 2–3 months postinjury	The presence of P300 after controlling for DRS and EEG reactivity		Diffuse body sweating in the acute phase
	Reactive EEG at 2–3 months postinjury			Epilepsy in the late phase
				Respiratory disturbance
				Flaccidity in the acute phase
Adult traumatic mixed (VS/UWS and MCS)		Faster improvements in DRS scores	Longer time post injury at study enrollment	
		Amantadine use	Worse DRS score at study enrollment	
			Dantrolene use	
		Left temporal lobe lesions, contusions/mass lesions, or subarachnoid hemorrhage on imaging	Left frontal or bilateral lesions on imaging	
Adult nontraumatic VS/UWS	CRS-R scores of ≥6 more than 1 mo after onset			
	Presence of SEPs			
Adult mixed traumatic and nontraumatic populations[a]	Approximate entropy value of ≥0.8 (vs <0.8)	Higher baseline composite score combining the CRS-R score plus points for DoC subtype		Older age
	Presence of MMN on EEG	Mental imagery fMRI		Longer length of time postinjury
		Increasing complexity of sleep architecture on PSG performed 3.5 ± 2 months postinjury		Abnormal early MLAEPs
				Presence of 3 or more medical complications during inpatient rehabilitation
Pediatric traumatic VS/UWS		Absence of posttraumatic autonomic dysfunction		Posttraumatic hyperthermia at any time

Abbreviations: CRS-R = Coma Recovery Scale–Revised; DRS = Disability Rating Scale; MCS = minimally conscious state; MLAEP = middle latency auditory evoked potential; MMN = mismatch negativity; SEP = somatosensory evoked potential; VS/UWS = vegetative state/unresponsive wakefulness syndrome.
[a] Some of these study cohorts are just patients with VS/UWS or MCS and some are mixed; see full guideline for details.

Prognostic factors for DoC subgroups are presented in table 3, with measures of association described in the full-length guideline. Nine studies[e4,e10,e20,e22,e25–e29] (links.lww.com/WNL/A612) (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 patients/study and thus were considered together.[e10,e25,e30] One Class II study[e29] and 1 Class III study[e31] examined prognostic factors for patients with traumatic DoC in populations where patients in VS/UWS and MCS were combined. Two Class I studies[e14,e28] and 2 Class II studies[e3,e22] examined prognostic factors for patients with

nontraumatic VS/UWS. Only 1 prognostic study[e28] was identified for patients in either traumatic or nontraumatic MCS; there was insufficient evidence to drive conclusions for either group. Two Class I studies[38,e5] and 7 Class II studies[e6,e8,21,e32–e35] examined prognostic factors in populations with mixed etiologies (traumatic vs nontraumatic) or mixed diagnoses (VS/UWS or MCS) or both in ways that individual subgroups could not be distinguished (table 3).

Prognostic factors in pediatric populations

In pediatric patients, traumatic (vs anoxic) etiology of VS/UWS present for at least 30 days is possibly associated with increased odds of recovery at 3–12 months (low confidence in the evidence, 1 Class II study[e36] [links.lww.com/WNL/A612]). A traumatic etiology, as compared to 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, as 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.

Therapeutic intervention

Two Class I therapeutic studies[e38,e39] (links.lww.com/WNL/A612) and 1 Class III therapeutic study[e40] were identified. Amantadine probably hastens functional recovery in patients with MCS or VS/UWS secondary to severe traumatic brain injury over 4 weeks of treatment (moderate confidence in the evidence, 1 Class I study[e38]) and appears safe in this population. 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). 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]), but the benefit of tilt table treatment vs placebo/nontreatment is not established (no identified studies).

Putting the evidence in a clinical context

The results of this systematic review highlight important gaps in knowledge related to diagnosis, natural history, prognosis, and treatment for patients with prolonged DoC. Some consistent weaknesses in study methodology were observed across studies, constraining the strength of the evidence. Small sample size was the most prevalent weakness due to limited study precision and generalizability.

In addition, the number of available studies was constrained by the a priori inclusion criteria of the guideline. The decision to include only studies investigating participants who were at least 28 days postinjury disqualified many studies conducted in the acute care setting, as well as those that either combined, or did not specify, the number of participants above and below this threshold. Some well-designed studies in which the majority of the participants met the 28-day inclusion criterion are considered in the rationale for recommendations as strong related evidence but could not contribute to the systematic review. Below, the guideline panel describes trends in study design within each of the 4 areas that compromised the strength of the evidence.

Diagnostic assessment

The most important challenge to validating more precise diagnostic approaches is the absence of an established reference (gold) standard with adequate sensitivity and specificity. The most commonly used reference standard (team consensus-based diagnosis) is associated with a 30%–40% error rate.[13–15] Thus, it is difficult to discern whether disagreement between the reference standard and a novel assessment measure reflects a false-positive or false-negative error on the part of the novel measure, or evidence that the novel measure has outperformed the reference standard. A second recurrent weakness in diagnostic studies is the infrequent use of masking procedures. Masking is essential to protect against examiner bias, which is particularly important when the assessment approach relies on nonobjective measures.

Natural history

Investigation of the natural history of recovery from severe brain injury requires a systematic approach to tracking selected milestones (e.g., mortality, recovery of consciousness, improvement in degree of disability). Many of the studies failed to report or control for the length of time from injury and instead anchored follow-up to date of admission to the inpatient rehabilitation setting. A study reporting that emergence from MCS occurs an average of 45 days after admission to the rehabilitation hospital is of limited clinical utility if the time to admission ranged from 4 to 52 weeks postinjury. Studies often failed to stratify or subanalyze participants by diagnostic subtype (VS/UWS vs MCS) and etiology (traumatic/nontraumatic), obscuring the trajectory of recovery. The fact that most natural history studies enroll participants at specialty rehabilitation centers is a further limitation, as these results may not generalize to individuals without access to specialty rehabilitation services.

Finally, relatively few natural history and prognostic studies reported long-term functional outcomes. In many studies, outcome assessment focused exclusively on recovery of consciousness or eMCS or both, without attention to the corresponding level of disability. Importantly, studies that tracked functional outcome beyond 1 year suggest up to 1 in 5 patients with prolonged DoC—especially those who transition to MCS before 6 months—eventually regain independence in the home environment[e41,e42] (links.lww.com/WNL/A612). DoC outcome research will be of greater relevance to clinicians, patients, and families by ensuring that results address the degree of functional improvement attained.

Prognostic assessment

The majority of studies investigating the predictive utility of patient and injury characteristics were conducted retrospectively, which subjected these studies to some of the same limitations noted in the natural history studies. Because inclusion criteria did not address specific clinical features known to be linked to outcome (e.g., diagnostic subtype, injury etiology, and length of time postinjury), within-sample variability tended to be high along these dimensions, contributing to wide CIs and imprecise outcome projection. In addition, risk factors and outcomes were often not assessed independently, allowing the possibility that factors believed to affect prognosis may have inappropriately influenced clinical decisions and contributed to unfavorable outcomes (including decisions to discontinue life-sustaining care).

Therapeutic interventions

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. First, the number of patients with prolonged DoC admitted to inpatient rehabilitation settings has progressively declined over the last 15 years. This trend is influenced by a number of factors, including a tendency by insurers to preferentially authorize rehabilitative care in lower-cost settings such as skilled nursing facilities. Consequently, it is difficult to enroll a large enough sample to support a sufficiently powered therapeutic study. Constraints on sample size also limit stratification of participants to account for differences in treatment effect related to mediating factors such as cause of injury, chronicity, and number of comorbidities.

A second challenge arises in the context of the rehabilitation setting. The typical length of inpatient rehabilitation in many academic medical centers has fallen below 20 days. Under these circumstances, family members are often reticent to enroll patients with prolonged DoC in a placebo-controlled trial in view of the 50% likelihood of assignment to the placebo arm, preventing any possibility of active treatment during rehabilitation apart from routine physical, occupational, and speech therapies.

Author contributions

Dr. Giacino: study concept and design, acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Katz: study concept and design, acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Schiff: study concept and design, acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Whyte: study concept and design, acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Ashman: acquisition, analysis, and interpretation of data, critical revision of the manuscript for important intellectual content. Dr. Ashwal: study concept and design, acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Barbano: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Hammond: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Laureys: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Ling: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Nakase-Richardson: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Seel: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Yablon: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. T. Getchius: acquisition, analysis, and interpretation of data. Dr. Gronseth: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Armstrong: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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His spouse has received an NIH grant unrelated to the content of this guideline. F. Hammond is a member of the ACRM Disorders of Consciousness Task Force; served on the US Department of Defence INTRuST Scientific Advisory Council and Avanir Prism II Study Steering Committee; has received royalties from Demos Publishing and Lash Publishing; has received financial support for research from the NIDILRR; holds stock in AbbVie Inc., Amgen Inc., AstraZeneca Plc, Edwards Lifesciences, GW Pharmaceuticals Plc, Intuitive Surgical Inc., Konink Logistics Inc., Merck & Co. Inc., Pfizer Inc., Sanofi, Thermo Fisher Scientific Inc., UnitedHealth Group, and Zoetis Inc.; and has given legal testimony and acted as legal consultant in legal proceedings on the care needs of individuals with brain injury. S. 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Conflict of interest

The American Academy of Neurology (AAN) and the American Congress of Rehabilitation Medicine (ACRM) are committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN and the ACRM keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN and the ACRM limit the participation of authors with substantial conflicts of interest. The AAN and ACRM forbid commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, at least 2 ACRM committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at aan.com. For complete information on this process, access the 2011 AAN process manual, as amended (aan.com/Guidelines/Home/Development).

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