Summary of Evidence-based Guideline for **Clinicians**

Practice Guideline Update: Disorders of Consciousness

This is a summary of the publication, "Practice guideline recommendations: Disorders of consciousness," which was developed through a collaboration of the American Academy of Neurology (AAN), the American Congress of Rehabilitation Medicine (ACRM), and the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR). This article was published in *Neurology*® and in *Archives of Physical Medicine and Rehabilitation* online on August 8, 2018, and in print on September 4, 2018.[1]

Please refer to the full guideline at *AAN.com/guidelines* for more information, including descriptions of the processes for classifying evidence, deriving conclusions, and making recommendations, and for details concerning upgraded or downgraded recommendations.

Disorders of Consciousness (DoC) Practice Recommendations

Unless otherwise noted, all recommendations specifically apply to the population addressed in this guideline (individuals with prolonged DoC, that is, DoC lasting 28 days or longer).

Recommendations Concerning the Adult Population

Recommendation 1

Rationale

Our systematic review has highlighted the complexities of caring for patients with a prolonged DoC (i.e., lasting 28 days or longer) at every stage, including diagnosis, prognosis, and treatment. Such patients may be misdiagnosed due to confounding neurologic deficits[2] or inexperience in examining patients for subtle signs of consciousness.[3] Accurate diagnosis is important to educate families about patients' level of consciousness and function, to inform prognostic counseling, and to guide treatment decisions. Knowledge gaps often lead to over- or under-estimation of prognosis by nonspecialists.[4] In addition, 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 DoC and are capable of initiating timely treatment. This is supported by findings from a large retrospective trauma registry which found that cumulative mortality at three years post discharge is significantly lower for patients discharged to home or inpatient rehabilitation facilities than those discharged to skilled nursing facilities, even after adjusting for covariates.[6] In the context of these diagnostic, prognostic, and treatment considerations, care for patients with prolonged DoC may benefit from a team of multidisciplinary rehabilitation specialists, which may include neurologists, psychologists, neuropsychologists, physiatrists, physical therapists, occupational therapists, speech pathologists, nurses, nutritionists, internists, and social workers.

Level B	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.

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 is 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 percent. Diagnostic error also includes misdiagnosing the locked-in syndrome (a condition in which full consciousness is retained) for vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious state (MCS).[14,15] Accurate diagnosis of the level of consciousness is important because of its implications for prognosis and management.

Additional Rationale 2a, Standardized and Specialized Behavioral Assessments

In view of the range of clinical challenges to accurate and reliable diagnosis of DoC, standardizing the assessment of patients with severe DoC can assist in recognizing key diagnostic features that may be missed on ad hoc examinations.[12,16] The validity and reliability of standardized neurobehavioral assessment scales for diagnosis of DoC subtype have been previously reviewed.[17] Other techniques, such as Individualized Quantitative Behavioral Assessment, have been useful in distinguishing specific purposeful responses from generalized, nonpurposeful, or reflexive responses.[18] On the basis of these findings, accuracy of diagnosis may be enhanced by using standardized neurobehavioral assessment measures in patients with prolonged DoC over qualitative bedside examination alone. If standardized assessments are used, those with the highest quality of evidence should be employed. A systematic review performed by the ACRM recommended the Coma Recovery Scale–Revised (CRS-R),[16] Wessex Head Injury Matrix,[19] Sensory Modality Assessment and Rehabilitation Technique,[20] Western NeuroSensory Stimulation Protocol,[21] the Disorders of Consciousness Scale,[22] and the Sensory Stimulation Assessment Measure[23] for use in clinical practice (with varying levels of confidence across measures).[17]

2a: Standardized and Specialized Behavioral Assessments

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.

Additional Rationale 2b, Serial Evaluations

While there is insufficient high-quality evidence to recommend the use of serial evaluations to improve the diagnostic sensitivity and specificity in patients with a DoC, because of the inconsistency and variability of behavioral responses that is characteristic of individuals with prolonged DoC, reliance on a single examination may contribute to a greater risk of misdiagnosis. Multiple behavioral evaluations over time may improve diagnostic reliability and accuracy compared with a single evaluation. Serial evaluations conducted by trained clinician(s) using a standardized, validated neurobehavioral assessment instrument have the potential to improve the reliability and validity of the diagnosis. There are insufficient data to recommend a minimum duration of time for an assessment session or how often serial examinations should be performed. The frequency of serial standardized neurobehavioral examinations should be based on clinical judgment, with consideration given to reported changes in arousal and responsiveness, the removal or cessation of diagnostic confounders, and the length of time since the last assessment.

2b: Serial Evaluations

Level B	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.

Additional Rationale 2c and 2d, Assessment and Enhancement of Arousal

Patients with prolonged DoC may exhibit inconsistent or reduced behavioral responsiveness because of fluctuations in the level of arousal, systemic medical problems (e.g., infections, metabolic disturbances), secondary neurologic complications (e.g., seizure, stroke, hydrocephalus, chronic subdural fluid collections), and other adverse events (e.g., medication side effects). The level of consciousness cannot be assessed accurately during periods of low arousal. In patients who demonstrate fluctuations in wakefulness, efforts should be made to increase arousal level using protocols designed for this purpose (e.g., Arousal Facilitation Protocol, see CRS-R Administration and Scoring Manual) before assessing the level of consciousness. Identifying and treating conditions that impair neurologic functioning may also improve arousal and level of consciousness.

2c and 2d: Assessment and Enhancement of Arousal

Level B	Clinicians should attempt to increase arousal before performing evaluations to assess level of consciousness any time diminished arousal is observed or suspected.
	Clinicians should identify and treat conditions that may confound accurate diagnosis of a DoC prior to establishing a final diagnosis.

Additional Rationale 2e and 2f, Use of Multimodal Evaluations

Our systematic review identified that some electrophysiologic procedures (specifically, EMG thresholds for detecting response to motor commands, electroencephalographic reactivity, laser evoked potential responses, and the transcranial magnetic stimulation–induced perturbational complexity index) possibly have value for distinguishing MCS from VS/UWS, generally to an only mildly important degree. There is currently insufficient evidence to support or refute the routine clinical use of functional neuroimaging (functional MRI [fMRI] or PET) or routine EEG or evoked response potential studies as clinically useful adjuncts to behavioral evaluations to detect conscious awareness in patients diagnosed with VS/UWS. In addition, functional imaging is not widely available and may not be clinically feasible in large numbers of patients. However, two reviewed studies[24,25] identified fMRI changes in response to a word-counting task and an incorrect-minus-correct activation protocol in patients diagnosed with VS/UWS by the CRS-R (38 percent, 95 percent confidence interval [CI], 14 percent to 69 percent, and 38 percent, 95 percent CI, 23 percent to 56 percent, respectively). Research studying DoC populations overlapping with those in this guideline (i.e., cohorts including patients with a DoC for longer than 28 days but not confined exclusively to patients with prolonged DoC) suggests that some individuals without signs of awareness on behavior-based evaluations may have positive findings using other modalities, such as functional MRI, PET scans, or electrophysiologic studies. In one study[26] of patients with VS/UWS based on standardized neurobehavioral assessment, functional neuroimaging studies (i.e., fluorine-18 fluorodeoxyglucose [^{18}F-FDG] PET, active fMRI) performed at various times post injury (from less than one month post insult to more than one year post insult) demonstrated evidence of brain activity compatible with at least minimal conscious awareness in approximately 32 percent of patients scanned using ^{18}F-FDG PET or mental imagery MRI or both (13 of 41, 95 percent CI, 20 percent to 47 percent), with ^{18}F-FDG PET showing results consistent with MCS in 33 percent of patients diagnosed with VS/UWS by the CRS-R (12 of 36, 95 percent CI, 20 percent to 50 percent) and mental imagery fMRI showing results consistent with MCS in 11 percent (3 of 28; 95 percent CI, 4 percent to 27 percent). When using high-density EEG recordings assessing a combination of low-frequency power, EEG complexity, and information exchange in a population overlapping with that in this guideline, 25 of 75 recordings in patients in VS/UWS (33 percent, 95 percent CI, 24 percent to 45 percent) were classified as suggestive of MCS, with a greater recovery of consciousness in those categorized as MCS than VS/UWS on the EEG (11 of 50 VS vs. 11 of 23 MCS, with two lost to follow-up; risk difference 26 percent, 95 percent CI, 3 percent to 47 percent).[27]

Although multimodal evaluations show promise in increasing sensitivity for detection of conscious awareness, these studies return negative findings in the majority of patients diagnosed with VS/UWS on behavioral assessment (see results just presented), and the exact link between these findings and consciousness remains unclear. Thus, widespread use of multimodal imaging is unlikely to change the diagnosis in most patients diagnosed with VS/UWS. At the same time, injury sequelae (such as severe hypertonus) may confound behavioral assessment and compromise diagnostic accuracy. Additionally, diagnostic findings may remain ambiguous despite serial assessment due to the inconsistency or subtlety of the behavioral evidence. The largest functional neuroimaging study conducted to date in patients with DoC reported that ambiguous or erroneous findings clouded clinical diagnosis in 33 of 126 (27 percent) of cases.[26]

2e and 2f: Use of Multimodal Evaluations

Level C	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.
	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 and decisions to reduce the intensity of rehabilitation treatment may be delayed for those individuals receiving active rehabilitation management, 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.

Recommendation 3

Rationale

In patients with severe traumatic brain injury (TBI), many of whom have a DoC, one study found that hospital mortality was 31.7 percent (95 percent CI, 28.4 percent to 35.2 percent), with 70.2 percent (95 percent CI, 63.9 percent to 75.7 percent) of those deaths associated with the withdrawal of life-sustaining therapy.[4] While certain clinical features may be helpful in predicting poor prognosis, this study found that withdrawal of care was more closely associated with the facility where care was provided than with baseline characteristics that included age, sex, pupillary reactivity, and Glasgow Coma Scale motor score.[4] While withdrawal of life-sustaining therapy in this TBI population was high, this systematic review identified that individuals with a DoC lasting longer than one month post injury may still attain functionally significant recovery after one year post injury. Additional research in populations overlapping those examined in the systematic review shows that patients with prolonged DoCs can achieve at least some degree of functional independence during long-term follow-up. For example, one study found that approximately 20 percent 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 one or more follow-up intervals (one, two, or five years).[28] Another longitudinal study including patients with both traumatic and nontraumatic DoC reported that almost half of the sample recovered to at least daytime independence at home and 22 percent returned to school or work.[29] While these studies examined patients at specialized rehabilitation centers and may not be fully generalizable, they suggest the potential for recovery in this population, which has implications for prognostic discussions.

Level A	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.

** This is the one recommendation in this guideline pertaining to individuals in a DoC for less than 28 days. While patients with an acute DoC are not the primary population covered by this guideline, the results of the systematic review and review of related evidence showing the potential for long-term recovery in individuals with DoC lasting longer than 28 days also apply when counseling the families of patients who are less than 28 days from injury.

Recommendation 4

Rationale

The natural history of DoC is not well defined, particularly for populations with nontraumatic DoC, and diagnosis and prognosis can be challenging. Individuals with DoC can fluctuate between different diagnostic categories such as VS and MCS. Fluctuation is particularly common early in the course of recovery,[3] and one study suggests a 30 percent (95 percent CI, 0 percent to 55 percent) 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.

Level B	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.

Recommendation 5

Rationale

In patients diagnosed with traumatic VS/UWS for at least a month, Disability Rating Scale (DRS) scores less than 26 at two to three months post injury, a detectable P300 at two to three months post injury, a reactive EEG at two to three months post injury, and higher-level activation of the auditory association cortex using blood-oxygen-level-dependent (BOLD) contrast fMRI in response to a familiar voice speaking the patient's name (performed one to 60 months post insult) probably have prognostic utility, suggesting an increased chance of recovering consciousness within 12 months. In this population, a normal single-photon emission computed tomography (SPECT) scan at one to two months post injury, lower DRS scores in general two to three months post injury, and a detectable P300 two to three months post injury after controlling for DRS and EEG reactivity are possibly associated with either an increased likelihood of recovery of consciousness or a more favorable outcome (less disability), while MRI imaging performed six to eight weeks post injury showing corpus callosal lesions, dorsolateral upper brainstem injury, or corona radiata injury is possibly associated with a worse prognosis (remaining in persistent VS [PVS]) at 12 months. In patients diagnosed with nontraumatic VS/UWS, specifically postanoxic VS/UWS, it is highly probable that CRS-R scores of 6 or greater at study entry (more than one month after onset) and the presence of somatosensory evoked potentials (SEPs; classified as present when N20 cortical response was recorded on at least one side, performed 4.6 months [± 3.8 months] post insult) from bilateral median nerve stimulation recorded with standard procedures each have prognostic utility as independent predictors of recovery, suggesting an increased likelihood of recovery of responsiveness by 24 months post injury. No prognostic models have been developed using these features as a composite to predict long-term outcome.

Level B	Clinicians should perform the DRS at two to three months post injury to assist in prognostication regarding 12-month recovery of consciousness for patients in traumatic VS/UWS.
	Clinicians should perform MRI six to eight weeks post injury 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.
	Clinicians should perform a SPECT scan one to two months post injury to assist in prognostication regarding 12-month recovery of consciousness and degree of disability/recovery for patients in traumatic VS/UWS.
Level C	Clinicians may assess for the presence of P300 at two to three months post injury or assess EEG reactivity at two to three months post injury to assist in prognostication regarding 12-month recovery of consciousness for patients in traumatic VS/UWS.
	Clinicians may assess for the presence of higher level activation of the auditory association cortex using BOLD fMRI in response to a familiar voice speaking the patient's name to assist in prognostication regarding 12-month (post-scan) recovery of consciousness for patients in traumatic VS/UWS one to 60 months post injury.

Recommendation 6

Rationale

In patients diagnosed with nontraumatic postanoxic VS/UWS, it is highly probable that CRS-R scores of 6 or greater obtained more than one month after onset and the presence of SEPs 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 post injury.

Level B	Clinicians should perform the CRS-R to assist in prognostication regarding recovery of consciousness at 24 months for patients in nontraumatic postanoxic VS/UWS.
Level C	Clinicians may assess SEPs to assist in prognostication regarding recovery of consciousness at 24 months for patients in nontraumatic postanoxic VS/UWS.

Recommendation 7

Rationale

The 1994 AAN Multi-Society Task Force defined VS as "permanent" three months after a nontraumatic insult 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 completed by nonaffiliated authors concluded the estimated rates of late recovery for traumatic and nontraumatic VS were unreliable due to inconsistent follow-up (i.e., only 27 cases were available with follow-up after 12 months), unreliable reporting (i.e., in some cases, follow-up was obtained through "personal communications"), 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] (which appropriately defined VS and reported findings on 25 cases followed after 12 months), six patients (14 percent) recovered consciousness between one and three years post injury. This recovery rate is substantially higher than the 1.6 percent reported in the Task Force Report and raised questions about the appropriateness of the term "permanent VS."

In the current systematic review, no study meeting inclusion criteria evaluated the prognosis of patients with traumatic VS/UWS after 12 months of injury, and individual case reports were not considered due to high risk of bias and an inability to calculate the frequency of recovery after 12 months. 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 two, three, four, and five years post injury (one was lost to follow-up, nine died, and two remained in VS/UWS), but due to the small sample size, CIs for the possibility of one improving were wide (0 percent, 95 percent CI, 0 percent to 24 percent).[34]

When considering patients with nontraumatic VS/UWS for at least one month, recent studies suggest that some patients may experience ongoing recovery after three months. Meta-analyses performed in this systematic review found it is possible that 17 percent (95 percent CI, 5 percent to 30 percent) will recover consciousness (emerge from VS/UWS) at six months, and that after six months, it is possible that an estimated 7.5 percent (95 percent CI, 0 percent to 24 percent) may recover consciousness from nontraumatic VS/UWS. In one study of prolonged anoxic vegetative state included in the systematic review, of the nine of 43 recovering responsiveness, two recovered between three and six months, three recovered at six to 12 months, and four recovered at 12 to 24 months, with the two individuals emerging from MCS falling in this later range (one 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). That is, of 41 patients who remained in VS/UWS at six months, seven additional patients recovered consciousness before 24 months (17 percent, 95 percent CI, 9 percent to 31 percent).[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, something accounted for in most but not all publications.

Additional evidence suggests that late transition to MCS from VS/UWS is not rare and may occur in as many as 20 percent of patients who meet permanence criteria. One long-term outcome study followed 50 patients who remained unconscious for a mean of 11.1 (± 4.8) months after traumatic or nontraumatic brain injury and reported that 10 patients (seven traumatic, three nontraumatic) recovered consciousness between 14 and 28 months post onset.[36] A second study followed 108 patients with TBI across a five-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 post onset, eight (47.0 percent) regained this ability between one and five years post injury.[28]

Although the majority of patients who remain in VS/UWS across the first three (after non-TBI) and 12 months (after TBI) post injury 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]

In view of the reanalysis of the data from the Multi-Society Task Force Report, and the results of the recent long-term outcome studies, 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 with 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.

Level B	Given the frequency of recovery of consciousness after three 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.

Recommendation 8

Rationale

Evidence from the prognosis section of the systematic review showed that in patients with prolonged DoC, those diagnosed with MCS within the first five 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 an MCS who have sustained traumatic vs. nontraumatic brain injury.[38] Age and time post injury are often considered in prognostic evaluations, but the evidence reviewed does not clearly support or refute these as prognostic features.

As described in the rationale for recommendation 3, evidence from the natural history section of the systematic review identified that individuals with a DoC at one month post injury may still attain functionally significant recovery after one year post injury, with additional longitudinal studies showing that approximately 20 percent of patients recover to the level where they could return to work or school.[28,29]

Level B	Clinicians should counsel families that MCS diagnosed within five 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.

Recommendation 9

Rationale

Patients with DoC lasting at least 28 days may have a prolonged recovery over months to years, and many will remain severely disabled. Employment and personal finances in both 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.

Level A	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.

Recommendation 10

Rationale

See rationale for recommendation 7.

Level B	When patients enter the chronic phase of VS/UWS (i.e., three 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.

Recommendation 11

Rationale

Pre-expressed 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.

Level A	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.

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 outcomes over the long term. The most common complications observed 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]

Level B	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.

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 currently 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.

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, 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.

Recommendation 14

Rationale

Amantadine (100 to 200 mg twice daily), when administered over a period of four weeks in patients between 16 and 65 years old with traumatic DoC who are between four 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.

Level B	Clinicians caring for patients with traumatic VS/UWS or MCS who are between four and 16 weeks post injury should prescribe amantadine 100 to 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.

Recommendation 15

Rationale

Most therapies proposed for treating patients with DoC (e.g., hyperbaric oxygen, nutraceuticals, stem cell therapies, primrose oil) have insufficient evidence to either support or refute their use, and many have associated risks. Families may pursue these treatments even in the absence of evidence because they are often desperate for ways to help their loved one, and because interventions supported by high-quality evidence are sparse. Counseling families about treatment effectiveness is further 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.

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.
	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.
	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.

Recommendations Concerning the Pediatric Population

Recommendation 16

Rationale

Using the same screening criteria applied to adults with prolonged DoC, 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 traumatic or hypoxic/ischemic DoC.

Level B	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.

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, while posttraumatic hyperthermia may be associated with a worse outcome. No other evidence regarding prognosis in pediatric DoC populations was identified.

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.

Recommendation 18

Rationale

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

Level B	Clinicians should counsel families that there are no established therapies for children with a prolonged DoC.

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This practice guideline update was co-developed by the American Congress of Rehabilitation Medicine and the National Institute on Disability, Independent Living, and Rehabilitation Research. The guideline was endorsed by the American Academy of Physical Medicine and Rehabilitation, by the American College of Surgeons Committee on Trauma, and by the Child Neurology Society.

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This document is a summary of the American Academy of Neurology (AAN), American Congress of Rehabilitation Medicine (ACRM), and the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) co-sponsored practice guideline "Disorders of Consciousness."

This research was supported through a memorandum of understanding between the AAN, the ACRM, and NIDRR. In 2014, NIDRR was moved from the US Department of Education to the Administration for Community Living of the US Department of Health and Human Services (HHS), and was renamed the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR). This article does not reflect the official policy or opinions of NIDILRR or the HHS and does not constitute an endorsement by NIDILRR, the HHS, or other components of the federal government.

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