Practice guideline update: 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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Approved by the AAN Guideline Development, Dissemination, and Implementation Subcommittee on October 21, 2017; by the AAN Practice Committee on April 9, 2018; by the

American Congress of Rehabilitation Medicine Board of Governors on April 30, 2018; by the National Institute on Disability, Independent Living, and Rehabilitation Research Review Committee on April 5, 2018; and by the AAN Institute Board of Directors on May 2, 2018.

This research was supported through a memorandum of understanding between the American Academy of Neurology, the American Congress of Rehabilitation Medicine and the National Institute on Disability and Rehabilitation Research (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, and was renamed the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR). This manuscript does not reflect the official policy or opinions of NIDILRR or HHS and does not constitute an endorsement by NIDILRR, HHS, or other components of the federal government.

This practice guideline was endorsed by the American Academy of Physical Medicine and Rehabilitation on April 4, 2018; by the American College of Surgeons Committee on Trauma on July 3, 2018; and by the Child Neurology Society on April 17, 2018.

STUDY FUNDING

This practice guideline was funded by the American Academy of Neurology (AAN), the American Congress of Rehabilitation Medicine, and the National Institute on Disability, Independent Living, and Rehabilitation Research. Authors who serve or served as AAN subcommittee members (E.J.A., S.A., R.B., G.S.G.) or as methodologists (M.J.A., G.S.G.), or who were AAN staff members (T.S.D.G.), were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

DISCLOSURE

J. Giacino has received funding for travel from the US Department of Defense for a meeting related to the TBI Endpoint Development Project; from the National Institute on Neurological Disorders and Stroke (NINDS) of the NIH for a meeting related to the Transforming Research and Clinical Knowledge in Traumatic Brain Injury study; from the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) for the Traumatic Brain Injury Model Systems Project Directors meeting; from the American Academy of Physical Medicine and Rehabilitation, the One Mind Foundation, and the James S. McDonnell Foundation for a meeting related to the Recovery of Consciousness After Severe Brain Injury study; from the Barbara Epstein Foundation, and from the International Brain Injury Association; has received a cash donation from the Epstein Foundation for a hospital clinical program that he directs and for serving on a team that provided clinical consultation services to an overseas patient who sustained severe brain injury; has served as an editor for the *Journal of Head Trauma Rehabilitation*; has received honoraria from the One Mind Foundation, Holy Cross Hospital (Surrey, United Kingdom); HealthSouth Braintree Hospital, Western Michigan Brain Injury Network, George Washington University Medical School, Association of Academic Physiatrists, Mayo Clinic, Kennedy-Krieger Institute, and *Magill's Medical Guide*; performs clinical procedures as 10% of his clinical effort in his role as Director of Spaulding Rehabilitation Network Disorders of Consciousness Program and neuroimaging as a principal investigator on 2 neuroimaging studies for 30% of his research effort; received financial support from the NIH NINDS for Central Thalamic Stimulation for Traumatic Brain Injury, US Department of Defense for TBI Endpoint Development Project, the Huperzine A for the Treatment of Cognitive, Mood and Functional Deficits After Moderate and Severe TBI study, the INjury and TRaumatic STress (INTRuST) Consortium Neuroimaging Acquisition and Archival study, the NIDILRR for the Spaulding Harvard - Traumatic Brain Injury Model System and for Multicenter Evaluation of Memory Remediation after traumatic Brain Injury with Donepezil, the NINDS for Transforming Research and Clinical Knowledge in Traumatic Brain Injury study, James S. McDonnell Foundation for Study of Recovery of Consciousness After Severe Brain Injury, Barbara Epstein Foundation, and the Spaulding Rehabilitation Hospital Department of Physical Medicine and Rehabilitation; and has acted as a witness with regard to a legal proceeding.

D. Katz has received royalties from Demos for *Brain Injury Medicine*, 2013, and from Lash Publications; has received honoraria for speaking at HealthSouth / Encompass Health Medical Directors' Conference, various grand rounds on topics related to disorders of consciousness

(DoC), including Harvard Longwood Neurology, Providence VA Hospital, Tufts Medical Center, Baystate Medical Center, and University of Massachusetts Medical Center, and for service as Chair, External Scientific Advisory Board, VA Rehabilitation Research and Development TBI Center of Excellence, Boston, Massachusetts; has given expert testimony in several legal cases involving patients with DoC after brain injury; has received travel support for talks and conferences on DoC from organizations, including World Federation of Neurorehabilitation, International Brain Injury Association, and Moody Foundation / Galveston Brain Injury Conference; received a stipend as medical director of the Acquired Brain Injury Program at Braintree Rehabilitation Hospital from HealthSouth; received compensation for less than 10% of his clinical effort for consultations on patients with DoC; and received support from efforts on NIDILRR-funded projects on DoC.

N. Schiff serves on an advisory board for Intelect Medical Inc. and Enspire DBS, Inc. (Cleveland, Ohio); is listed as inventor for multiple patents held by Cornell University; receives royalties for Plum and Posner's *Stupor and Coma*, Oxford University Press; and holds 0.25% stock option in Enspire DBS, Inc (no current value).

J. Whyte served on a scientific advisory board for INTRuST; received funding for travel and honoraria from several noncommercial institutions for academic lectures; performs diagnostic behavioral assessments of patients with DoC as 10% of his clinical effort; received financial support from the NIH, the NIDILRR, and the Patient-Centered Outcomes Research Institute; and has given expert testimony with regard to a patient with DoC.

E. Ashman served as Level of Evidence associate editor for the *Neurology* journal from 2011−2013; provided uncompensated medical-legal reviews for US Air Force legal proceedings as part of his active-duty responsibilities until 2012; received funding from the American Academy of Neurology (AAN) to attend Guideline Development, Dissemination, and Implementation Subcommittee meetings as a subcommittee member and as an ex officio member through January 2018; and has been selected to serve on the editorial board of *Neurology: Clinical Practice* starting April 2018.

S. Ashwal served on a medical advisory board for the Tuberous Sclerosis Association; serves as chief of the Division of Child Neurology, Department of Pediatrics, Loma Linda University School of Medicine; receives royalties for *Pediatric Neurology: Principles and Practice*, 6th ed.; received financial support from the NIH NINDS for research on pediatric traumatic brain injury and for use of advanced imaging for detecting neural stem cell migration after neonatal HII in a rat pup model.

R. Barbano has served as the associate editor for *Neurology: Clinical Practice*; has received compensation from law firms and insurance companies for independent medical records reviews and examinations; holds stock options from Visual Dx, Inc.; served on a speakers bureau for Allergan Inc.; and receives research support from the NIH Office of Rare Diseases Research via the Dystonia Coalition, unrelated to the content of this guideline. 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. Laureys performs fMRI, PET, and EEG as 20% of his clinical effort; received funding from noncommercial institutions such as Belgium's National Fund for Scientific Research, European Commission, Collaborative European NeuroTrauma Effectiveness Research in TBI Project, Human Brain Project, James McDonnell Foundation, European Space Agency, "Fondazione Europea di Ricerca Biomedica", BIAL Foundation, Belspo, Wallonia-Brussels Federation Concerted Research Action and Mind Science Foundation; has served as an editor for *Progress in Brain Research* and *Current Opinion in Neurology*; is a member of the Belgian Advisory Committee on Bioethics and Belgian Brain Council, board member of the International Brain Injury Association; elected delegate of the European Academy of Neurology; President of the Association for the Scientific Study of Consciousness and chair of the World Federation of Neurology Applied Research Group on Coma and Disorders of Consciousness; receives royalties for *The Neurology of Consciousness*, Elsevier 2015; has given expert testimony with regard to legal cases in Belgium and The Netherlands; and has prepared an affidavit and acted as a witness for legal proceedings in Belgium.

G. Ling has served on scientific advisory boards for the NIH National Center for Advancing Translational Sciences (NCATS), the Veterans Administration National Research Advisory Council, Biogen, Facebook B8, KnoLimits, LLC, NED Biosystems, and Camden Partners; served on the board of directors of BioElectron Technologies Corporation (aba Edison Pharmaceuticals); received funding for travel from NIH NCATS, Facebook B8, Edison Pharmaceuticals, KnoLimits, LLC, and Camden Partners; served as a guest editor for *Seminars in Neurology* and *Experimental Neurology*; holds a patent (U.S. Patent 7, 195, 595-B2) with Campbell, M., for a method and apparatus used for monitoring the efficacy of fluid resuscitation; received honoraria from Medtronics, National Defense University (Japan), Sanofi Aventis, Science Teachers, and University of Panama (Panama); has been employed by SunQLLC, DrsGSLing, and Center for Brain Health; and holds stock in BioElectron Technologies Corporation (aba Edison Pharmaceuticals), Host Response, NED Biosystems, Camden Partners, Pfizer, and Merck.

R. Nakase-Richardson has received financial compensation for travel for speaking at the University of Mississippi Medical Center, New York University, Mayo Clinic, and University of Alabama, Birmingham; has received research support from General Dynamics Health Solutions from the Defense and Veterans Brain Injury Center within the Defense Health Agency, US Department of Veterans Affairs Health Services Research and Development, Department of Veterans Affairs Rehabilitation Research and Development, and Patient-Centered Outcomes Research Institute.

R. Seel has served as both a member and the Chair of the ACRM Disorders of Consciousness Task Force and the ACRM Evidence and Practice Committee; served as an editor for the *Journal of Head Trauma Rehabilitation*; holds a patent on an electronic driving coach; receives publishing royalties from Pearson; received honoraria for several university-based talks; received payment as a grant reviewer for the Department of Defense Congressionally Directed Medical Research Programs and US Department of Veterans Affairs Rehabilitation Research and Development Service; and has received research funding from the NIDILRR, the NIH, the Centers for Disease Control and Prevention, the Craig H. Neilsen Foundation, and the Shepherd Center Foundation.

S. Yablon has served on scientific advisory boards for Allergan Inc., Flowonix Medical Inc., Ipsen Pharma, Medtronic Inc., and Merz Pharmaceuticals GmbH; received travel-related funding from Allergan Inc., Ipsen Pharma, Medtronic Inc., and Merz Pharmaceuticals GmbH; served as associate editor for the journal *PM&R* and on the editorial advisory board for the Baylor University Medical Center Proceedings; has received honoraria for presentations given during scientific meetings sponsored or cosponsored by Allergan Inc. and Merz Pharmaceuticals GmbH; performs botulinum neurotoxin procedures for treatment of focal spastic hypertonia (< 10% of clinical effort); has received financial research support from Medtronic Inc. and research support from the NIDILRR; and has given expert testimony and acted as legal consultant in legal proceedings.

T. Getchius has received financial compensation for travel to speak at the University of Louisville mTBI conference and the New York Academy of Medicine E-GAPPS conferences; has been serving as the vice-chair of the Council of Medical Specialty Societies Clinical Practice Guideline Component Group from November 2013 to present; has received research support (all monies directed to the AAN) from the CDC for a grant for muscular dystrophy guideline development, dissemination, and implementation; and is a past employee of the AAN.

G. Gronseth serves on the *Neurology Now* editorial advisory board and receives financial support for serving as chief evidence-based methodologist for the AAN.

M. Armstrong serves on the Level of Evidence editorial board for *Neurology* (but is not compensated financially) and serves as an evidence-based medicine methodologist for the AAN.

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.
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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.

ABBREVIATIONS

Aδ-LEP: Aδ-fiber LEP
AAN: American Academy of Neurology
ABI: acquired brain injury
ACRM: American Congress of Rehabilitation Medicine
pEn: approximate entropy
AUC: area under the curve
BAEP: brainstem auditory evoked response
BDNF: brain-derived neurotrophic factor
BOLD: blood oxygen level dependent
C-LEP: C-fiber LEP
COI: conflict of interest
CRS-R: Coma Recovery Scale-Revised
DAI: diffuse axonal injury
DBS: deep brain stimulation
DF: degrees of freedom
DoC: disorders of consciousness
DOCS: Disorders of Consciousness Scale
DRS: Disability Rating Scale
DTI: diffusion tensor imaging
EMCS: emergence from MCS
ERP: evoked response potential
FDG: fluorodeoxyglucose
FIM: functional independence measure
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
GOSE: Glasgow Outcome Scale–Extended
GRADE: Grading of Recommendations Assessment, Development and Evaluation
IPL: interpeak latency
LEP: laser-evoked potential
LIS: locked-in syndrome
LR: likelihood ratio
MCS: minimally conscious state
MLAEPs: middle-latency auditory evoked potentials
MMN: mismatch negativity
MSTF: Multi-Society Task Force
NC: normal control
NLPO: non–phase-locked oscillations
OR: odds ratio
PC-U: post-coma unawareness
PCI: Perturbational Complexity Index
PPV: positive predictive value
PTCS: posttraumatic confusional state
PVS: persistent vegetative state

qEEG: quantitative EEG
ROC: receiver operating curve
SD: standard deviation
SEP: somatosensory evoked potential
TBI: traumatic brain injury
TMS: transcranial magnetic stimulation
UWS: unresponsive wakefulness syndrome
VS: vegetative state

ABSTRACT

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

Methods: Articles were classified per the AAN evidence-based classification system. Recommendations were based on evidence, related evidence, principles of care, and inferences according to the AAN 2011 process manual, as amended.

Results and recommendations: Limited evidence exists regarding optimal diagnosis, expected natural history, and appropriate treatment of disorders of consciousness; more studies have examined prognostic features. Based on the frequency of recovery of consciousness after 3 months in patients in nontraumatic vegetative state/unresponsive wakefulness syndrome (VS/UWS), and after 12 months in patients with traumatic VS/UWS, 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). No evidence was identified to support or refute a change in the MCS case definition. Additional recommendations cover current strategies for diagnosing, assessing prognosis, and treating patients with disorders of consciousness alongside patient and family preferences and also cover important topics for counseling families.

In simplest terms, consciousness is defined as the state of awareness of the self and environment.[e1] 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)[e2] and the minimally conscious state (MCS).[e3] VS is also referred to as post-coma unawareness (PC-U)[e4] or unresponsive wakefulness syndrome (UWS).[e5] 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 provides the definitions for VS and MCS and other key terms pertinent to DoC.

The incidence and prevalence of VS and MCS in the United States are difficult to estimate because of the lack of formal surveillance outside of specialty care settings. The incidence of MCS is unknown largely because a diagnostic code has not been assigned to this condition for inclusion in the International Classification of Diseases morbidity classification system (World Health Organization). Prevalence estimates for both conditions are hampered by economic factors that lead patients with DoC to be transferred to long-term care facilities following discharge from the acute care setting. Based on available epidemiologic data,[e6] the annual incidence of VS is approximately 4,200 persons. Prevalence estimates are highly variable, ranging from 5,000 to 42,000 persons.[e7-e9] Prevalence estimates for MCS are believed to be much higher (112,000 to 280,000 persons), but these figures are based on a proxy definition for MCS derived from a California state registry for persons with developmental disabilities.[e10]

Recently, investigators have proposed that MCS be dichotomized into MCS+ and MCS- on the basis of the presence or absence of signs of preserved language function (e.g., command-following or intelligible speech).[e11] Emergence from MCS (EMCS) occurs when there is recovery of reliable yes/no communication or functional object use (i.e., the ability to demonstrate instrumental use of at least 2 different familiar objects) (table e-1).[e3] VS/UWS and MCS usually represent transitional states between coma and consciousness, but either VS/UWS or MCS may become permanent.[e12] Accurate differential diagnosis is critically important to clinicians and family members, as there is mounting evidence that patients diagnosed with MCS early in the course of recovery (i.e., within 3 months) achieve significantly more favorable functional outcomes by 12 months post injury compared with those diagnosed with VS.[e13-e15]

The cost of lifetime care for persons with prolonged DoC can exceed $1,000,000.[e16] 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)[e17] following an evidence-based review of the literature completed by the Multi-Society Task Force (MSTF) on PVS.[e2] In 2002, the Aspen Neurobehavioral Workgroup defined MCS and published consensus-based diagnostic criteria for this condition.[e3] Both reports focused on diagnosis, and only the MSTF report discussed prognosis. Data addressing treatment were sparse, and thus neither report was able to provide clear guidance on specific interventions.

Since publication of the diagnostic guidelines for VS/UWS and MCS, the pace of research on DoC has advanced rapidly, but estimates of misdiagnosis (e.g., VS/UWS vs MCS) among patients with DoC remain consistently high, approximating 40%.[e18-e20] In a US study,[e19] 18 of 49 patients admitted to an inpatient rehabilitation unit with a referring diagnosis of "coma" or "persistent VS" were confirmed to have at least 1 behavioral sign of consciousness by 2 board-certified neurologists within 72 hours of admission. In a European study[e20] enrolling patients who were at least 6 months post onset and carrying a referral diagnosis of "VS," an incorrect admitting diagnosis was demonstrated in 43% (17/40) of patients after consistent command-following was detected by at least 2 members of the rehabilitation team. Misdiagnosis resulted from unrecognized visual or visuoperceptual disorders and severe motor impairment interfering with detection of command-following, as revealed through use of adaptive equipment. In 2009, a large, prospective, multicenter European study[e18] found that of 44 patients with a consensus-based diagnosis of VS/UWS, 18 (41%) met criteria for MCS on reevaluation by the research team within 24 hours using a standardized assessment measure. In the most recent study,[e18] 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 within 24 hours using a standardized neurobehavioral assessment scale. In addition, 89% of those who had an uncertain diagnosis (n = 18) were found to have clear signs of consciousness on standardized examination. Findings from the other 2 studies[e19,e20] were in the same direction. The most common cause of misdiagnosis was failure to detect visual pursuit. These error rates underscore the need for more refined diagnostic evaluation methods. In addition, some investigators have recommended that the criteria for EMCS be revisited, citing data that support the premise that existing criteria may lead to overdiagnosis of this condition.[e21]

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,[e22] a growing body of research suggests that functional neuroimaging techniques, such as fMRI and PET, may be able to detect imaging changes that suggest conscious awareness in the absence of bedside evidence.[e23-e26]

Natural history studies of patients with prolonged DoC now include outcomes extending beyond 1 year, which provides an opportunity to reassess the 1994 MSTF introduction of the term *permanent VS* (table e-1), which is questioned based on the methodology used to calculate the incidence of recovery of consciousness beyond 12 months[e27] and the total number of individuals available for follow-up after 12 months (i.e., 30).[e28] Increasing publications are also available for DoC prognosis and treatment.

The effectiveness of treatment interventions designed for individuals with prolonged DoC has been the subject of few rigorous studies, but results of multicenter randomized trials are now becoming available for this population.

The purpose of this practice guideline and its accompanying systematic review was to update the 1995 AAN guideline on PVS[e17] and the 2002 case definition on MCS.[e3] The guideline targets nonexpert neurologists and rehabilitation specialists who care for persons with prolonged DoC.

The guideline panel expects the conclusions and recommendations will also be of interest to clinical experts and researchers in this field as they investigate the effectiveness of traditional (e.g., behavioral examination) and novel (e.g., functional neuroimaging) assessment procedures and treatment interventions (e.g., pharmacotherapy). This review aims to answer 10 clinical questions concerning patients with traumatic and nontraumatic DoC (table e-2), which are broadly stated as follows: (1) What procedures accurately diagnose prolonged DoC? (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, where prolonged DoC is defined as lasting at least 28 days? Studies of pediatric populations were included in the review and were subjected to the same review criteria as used for the studies of adults.

Recommendations for pediatric populations are listed separately from recommendations for adult populations. This guideline does not apply to patients in the acute setting who are less than 28 days post injury.

DESCRIPTION OF THE ANALYTIC PROCESS

This practice guideline was developed in accordance with the process described in the 2011 AAN Clinical Practice Guideline Process Manual, as amended.[e29] In July 2011, the AAN Guideline Development, Dissemination, and Implementation Subcommittee, in conjunction with the American Congress of Rehabilitation Medicine Board (ACRM) and the National Institute on Disability and Rehabilitation Research, convened a panel of authors with a range of expertise, including neurology, neuropsychology, physiatry, and AAN guideline development (see appendices e-1 through e-4). Each potential author was required to submit an online conflict of interest (COI) form and a copy of his or her curriculum vitae (CV). The panel leadership, consisting of the lead author (J.T.G.), an AAN methodologist (G.S.G.), and an AAN staff person (T.S.D.G.), reviewed the COI forms and CVs for financial and intellectual COI. These documents were specifically screened to exclude those individuals with a clear financial conflict and those whose profession and intellectual bias would diminish the credibility of the review in the eyes of the intended users. As required by AAN policy, the lead author (J.T.G.) had no COIs as defined at project initiation. The panel then devised clinical questions related to the diagnosis, prognosis, and treatment of persons with prolonged DoC. Guideline development was supported by the work of 2 methodologists (G.S.G., M.J.A.). A representative from the Brain Injury Association of America provided insight on behalf of patients and families.

The panel developed a protocol that was posted on the AAN Web site (https://www.aan.com/Guidelines/Home/PublicComments) for a 30-day public comment period (September 2012), after which time all comments received were acknowledged and reviewed in order to refine the clinical questions in preparation for a second literature search and data extraction.

In 2012, the panel contracted with a medical librarian to perform literature searches of the MEDLINE, Science Citation Index, and EMBASE databases to locate relevant articles published from 1950 to 2012 (MEDLINE), 1960 to 2012 (Science Citation Index), and 1980 to 2012 (EMBASE); this search was then updated in November 2015 and again in February 2017 to

identify additional articles published after the initial search. The key text and index words used in the search are presented in appendix e-5. The search included peer-reviewed articles on humans, regardless of the language of the publication, and conference abstracts. When relevant abstracts written in languages other than English were identified, the method sections of the associated articles were translated into English and reviewed for inclusion.

The original database search yielded 15,241 titles and abstracts, all of which were reviewed by at least 2 panel members independently. Of the 15,241 abstracts identified, 369 were deemed relevant and the corresponding articles obtained. At least 2 panelists working independent of each other reviewed the full text of these articles and selected 126 for full analysis. In the 2015 update, 5,418 abstracts were identified, 246 were deemed relevant, and, after reconciliation of abstracts, the articles corresponding to 132 of these abstracts were selected and obtained for full text analysis. In the 2017 update, 1,018 abstracts were identified, and 113 were deemed relevant and the corresponding articles obtained for full text analysis.

Panel members extracted the relevant information from these articles using standardized data extraction forms based on the 2011 AAN schemes for classification of screening, diagnostic, and prognostic studies; the panel used the revised scheme for classifying therapeutic studies in the 2011 process manual, as amended[e29] (see appendix e-6). Data extraction forms were developed by AAN methodologists and completed by panel members using Google Docs. Disagreements were reconciled by discussion, or, when not feasible, a third panel member arbitrated differences in ratings, either by reviewing the paper independently or by reviewing the specific topic of disagreement. The class of each study was either automatically calculated by a spreadsheet populated from the data extraction forms or assigned by 2 AAN methodologists on the basis of the extractions and additional review of the articles, if needed.

Inclusion criteria relevant for all questions were as follows: (1) population had a DoC for at least 28 days (i.e., prolonged DoC) and (2) the study enrolled at least 20 patients with a prolonged DoC. The minimum sample size was selected a priori, as smaller studies have limited precision and generalizability. The minimum cutoff for inclusion was 28 days post injury to ensure that patients in coma were excluded (the vast majority of patients emerge from coma within 21 days). Patients in coma are distinct from the target population (VS/UWS, MCS, EMCS) in several ways: the diagnostic features are well recognized, the natural history of recovery is well known (i.e., it resolves within 4 weeks of onset, with rare exception), and outcomes are highly variable (unlike outcomes for patients with prolonged DoC, who are typically left with moderate to severe disability). In addition, articles were accepted only if the entire subject 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 that included potentially relevant data. This is discussed further in the section "Putting the Evidence in a Clinical Context."

After data extraction, the guideline authors synthesized the evidence and developed conclusions according to the AAN's modified form of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process,[e30] considering precision, consistency, directness, plausibility, magnitude of effect, and dose response, where relevant, as required by

the 2011 AAN process manual, as amended.[e29] Only articles with a classification of evidence higher than Class IV were considered in the development of conclusions.

Classification of evidence for risk of bias followed the 2011 process manual, as amended (appendix e-7). For diagnostic imaging studies that did not explicitly indicate whether masking procedures were used, the guideline panel decided to assume that the clinicians who interpreted the imaging and neurophysiologic results did so independently of those who performed and interpreted the behavioral outcome measures. For diagnostic studies, only data pertaining to persons with a possible DoC were considered; data comparing persons with DoC with a normal control group were not described because of the absence of any diagnostic uncertainty in that comparison. Natural history studies were classified on the basis of an adaptation of the AAN's screening criteria.[e29] Studies were excluded from the natural history section if outcomes were not systematically assessed at specific time points. For prognostic studies, categorization of the class of evidence was based on the most objective outcome (typically death) rather than for each outcome independently, as it was judged unlikely that investigators would misclassify someone as recovering consciousness based on the knowledge of the multitude of possible predictor variables reported in most prognostic studies.

In assessing precision during the modified GRADE evidence synthesis, the guideline panel downgraded any CI that included no effect (which would correspond to a nonsignificant *p* value; e.g., the CI of an odds ratio [OR] crossed 1). For diagnostic studies, the panel reviewed or calculated sensitivity, specificity, and the positive likelihood ratio (LR+) as measures of diagnostic accuracy. Application of the modified GRADE process was performed using LR+, as this measure combines sensitivity and specificity. According to convention, LRs > 5 and < 0.2 were considered moderately important and LRs 0.5–2 were considered unimportant. For example, a test result with a LR+ > 10 indicates that this result is 10 times more likely to be seen in a patient who has the target condition (e.g., MCS) than it is in a patient who does not. Conversely, the further the LR falls below 1, the less likely the patient is to have the condition (e.g., a test result with an LR+ < 0.1 nearly rules out the possibility that the patient has the condition). When assessing precision for the modified GRADE process in studies with a statistically significant LR+, the guideline panel downgraded confidence by 1 if the lower CI was in the unimportant range (< 2). When deciding whether to recommend against a test of diagnostic accuracy in the circumstance of LR+s that were not statistically significant, the panel downgraded confidence by 1 if CIs included values of slight importance (0.2–0.5, 2–5) and by 2 if CIs included values of moderate importance (< 0.2, > 5), suggesting the study could not exclude the possibility of important implications for diagnosis.

No results were downgraded for precision when assessing natural history, but CIs were provided for each conclusion. For the prognosis section, the decision was made *not* to downgrade when the CIs around ORs were consistent with statistical significance but contained values of uncertain clinical relevance (e.g., an OR of 1.05). These CIs are presented in a transparent manner for individuals to make their own judgments. However, when these CIs included ORs of uncertain clinical relevance, confidence was not upgraded for magnitude of effect regardless of the point estimate of the OR. Only 1 high-quality treatment study was identified, and the statistically significant results of this study are noted.

Recommendations were developed using a modified Delphi process following the AAN methodology.[e29] The guideline panel anchored recommendations in the evidence but also considered strong related evidence, principles of care, inferences, benefits relative to harms, importance of outcomes, variation of patient preferences, feasibility and availability of the intervention, and cost. The panel drafted and revised recommendations and subjected them to 3 rounds of modified Delphi electronic voting to achieve consensus and determine the strength of each recommendation. This process is documented in appendices e-8 through e-10. Each recommendation is accompanied by a level describing the strength of the recommendation, with Level A denoting a strong recommendation, Level B a moderate recommendation, and Level C a weak recommendation.

This document is divided into 4 sections: Analysis of Evidence (the systematic review), Putting the Evidence in a Clinical Context, Practice Recommendations, and Suggestions for Future Research. The analysis of evidence is divided into 4 subsections: diagnosis, natural history, prognosis, and treatment. In each subsection, the relevant evidence is presented, followed by conclusions. After a discussion of the clinical context for the evidence, the document concludes with the recommendations for clinical care and suggestions for future research. Each of the 18 recommendations first describes the rationale for the recommendation and then presents a recommendation statement. The last 3 recommendations (i.e., 16–18) specifically pertain to the pediatric population.

The draft guideline was reviewed by the AAN Guideline Development, Dissemination, and Implementation Subcommittee on multiple occasions in accordance with the AAN methodology. The draft guideline was also reviewed by members of the ACRM and was posted on the AAN Web site (https://www.aan.com/Guidelines/Home/PublicComments) for a 30-day public comment period in September 2017. All comments were addressed before finalization of the guideline.

ANALYSIS OF EVIDENCE

Diagnostic assessment

For the diagnostic question, the guideline panel considered patients with traumatic VS/UWS or nontraumatic VS/UWS or MCS at least 28 days post-injury and asked if any diagnostic assessment procedures that incorporate the Aspen Neurobehavioral Workgroup criteria accurately detect behavioral signs of consciousness or differentiate specific DoCs (VS/UWS, MCS, and posttraumatic confusional state [PTCS]) compared with consensus-based diagnostic opinion or standardized behavioral assessment. Readers are referred to a previously published systematic review completed by the ACRM Disorders of Consciousness Task Force that provides evidence-based recommendations for clinical use of standardized behavioral assessment methods.[e22] Despite differences in methodology relative to the current project, in view of the rigor and comprehensiveness of the ACRM Task Force work, the guideline panel elected not to repeat this effort. The panel also asked whether there is sufficient evidentiary support for the existing criteria for EMCS and whether serial evaluations or evaluation by an expert differentiate

specific DoCs with greater sensitivity and specificity relative to consensus-based diagnosis. Finally, the panel asked whether functional imaging or electrophysiologic procedures compared with standardized behavioral evaluations add to sensitivity and specificity in distinguishing specific DoCs.

The guideline panel reviewed 249 articles for the diagnostic questions, of which 60 met inclusion criteria. Of these, 8 articles were Class I for at least some diagnostic procedures,[e31-e38] 4 articles were Class II,[e33,e39-e41] and 4 articles were Class III.[e42-e45] Results are summarized below and organized by type of diagnostic procedure.

No qualifying studies with evidence rated greater than Class IV were identified to address the diagnostic validity of standardized and nonstandardized behavioral assessment procedures for detection of conscious awareness. There was also insufficient evidence to establish the diagnostic utility of serial evaluations, use of expert vs novice examiners, procedures that incorporate the Aspen criteria, or the appropriateness of the existing behavioral criteria required to establish emergence from MCS.

Electromyography

Two Class I studies investigated the use of EMG for detecting responses to command. The first study[e31] (Class I for the comparison of VS/UWS and MCS) enrolled 38 patients (10 VS/UWS, 28 MCS) with DoCs of various etiologies. Given the presence of involuntary activity (e.g., hypertonicity), a secondary analysis was performed to identify when the increased activity was significantly higher for the area corresponding to the command's target area (arm, leg, jaw), compared with activity during other commands, to ensure the EMG activity was command-related. With this analysis using a Bonferroni adjustment, a response to command was identified in only 1 patient with VS/UWS and 3 patients with MCS+ (sensitivity for MCS 21%, 95% CI 5%–51%, specificity 90%, 95% CI 56%–100%; LR+ 2.14, 95% CI 0.26–17.72). The second study[e37] used a ratio between a response to motor commands and a control command to distinguish voluntary responses from involuntary, reflexive, or spastic movements. Using a threshold score of 1.5, 0 of 15 patients with VS/UWS, 2 of 8 patients with MCS-, and 14 of 14 patients with MCS+ demonstrated an EMG response to motor commands. A positive (above threshold) EMG response thus corresponds to a sensitivity of 73% (95% CI 50%–89%), specificity of 100% (95% CI 78%–100%), and an LR+ (using a continuity correction) of 23.0 (95% CI 1.5–355.6) for distinguishing MCS (MCS- or MCS+) from VS/UWS.

Electroencephalography

Two Class I studies evaluated EEG for diagnosing type of DoC. The first study[e33] (rated Class I for EEG data and Class II for fMRI data) enrolled 31 patients with VS/UWS and MCS of various etiologies, 6 months to 26 years post injury. On awake EEG recordings, patients in MCS often had normal or only mildly abnormal EEG background rhythms (14/23; 61%, 95% CI 41%–78%; 4 of 6 patients with MCS- and 10 of 17 patients with MCS+). Two of 8 patients in VS/UWS also demonstrated normal or mildly abnormal findings (25%, 95% CI 7%–59%). Sensitivity for a diagnosis of MCS (vs VS) in the setting of a normal or mildly abnormal EEG background

rhythm was 61% (95% CI 39%–80%) and specificity was 75% (95% CI 36%–96%). LR+ was 2.43 (0.70–8.45). One patient with MCS+ had severely abnormal awake EEG background (1/14, 7%, 95% CI 1%–31%).

A second EEG study[e35] analyzed EEG activity and reactivity to eye opening and closing in response to different sensory stimuli in 37 patients with VS/UWS and 36 patients with MCS (11 MCS-, 25 MCS+) of traumatic, vascular, or anoxic etiologies. In this study, 12 of 36 patients with MCS had normal or mildly abnormal EEG backgrounds (33%, 95% CI 20%–50%, 1/11 MCS- and 11/25 MCS+) vs 0 of 37 patients with VS/UWS (0%, 95% CI 0%–9%). The sensitivity of a normal or mildly abnormal EEG background rhythm for a diagnosis of MCS (vs VS/UWS) was 33% (95% CI 19%–51%), specificity was 100% (95% CI 88%–100%), and LR+ was 25.7 (95% CI 1.6–418.1) using a continuity correction. Poor EEG organization (categorized as moderately abnormal, diffuse slowing, or low voltage) was present in the remaining patients, with 1 patient in MCS+ identified has having low voltage. A random-effects meta-analysis of the sensitivity and specificity values from these 2 studies resulted in a sensitivity of 46% (95% CI 19%–74%, I^2 = 78%), specificity of 92% (95% CI 69%–100%, I^2 = 61%), and LR+ of 5.6 (95% CI 0.6–51.3, I^2 = 57%) when assessing the value of normal or mildly abnormal EEG background rhythm for a diagnosis of MCS (vs VS/UWS).

The second EEG study[e35] also evaluated the utility of EEG reactivity to eye opening and closing, to tactile, painful, and acoustic stimulation, and to intermittent photic stimulation. Eighteen of 37 patients with VS/UWS and 35 of 36 patients with MCS had reactivity to at least 1 sensory stimulus (sensitivity for MCS 97%, 95% CI 85%–100%; specificity 51%, 95% CI 24%–68%; LR+ 2.00, 95% CI 1.43–2.80). Results were similar when using reactivity to at least 1 stimulus type to distinguish VS/UWS from MCS-, where sensitivity was high (91%, 95% CI 59%–100%) for diagnosing MCS- in the presence of EEG reactivity but specificity was low (51%, 95% CI 34%–68%). Other EEG reactivity results are also described in the study but not presented here. Of note, patients with anoxic DoC were generally less responsive to stimuli than patients with traumatic or vascular insults. Combining a low-voltage background EEG pattern and the lack of EEG reactivity better distinguished VS/UWS from MCS-. This combination was present in 20 of 37 patients with VS/UWS and 1 of 10 patients with MCS-, resulting in high sensitivity for a diagnosis of VS (91%, 95% CI 59%–100%), with a specificity of 54% (95% CI 37%–71%) and an LR+ of 5.4 (95% CI 0.82–35.5).

One Class III study[e42] used EEG entropy, a metric that describes the irregularity, complexity, or unpredictability of a stochastic EEG signal, to differentiate patients who were unconscious from those who were minimally conscious in a group of 56 patients with traumatic and nontraumatic DoCs. Analysis of the 27 patients who were > 28 days post injury revealed that the sensitivity and specificity of the receiver operating curve (ROC) analysis were too low to reliably differentiate patients who were conscious from those who were unconscious (area under the curve [AUC] 0.5; 95% CI 0.3–0.8; data insufficient for calculating other measures of diagnostic accuracy).

Evoked potentials

A Class I study[e38] used laser-evoked potentials (LEPs), which selectively activate nociceptive pathways, and measured N1P1 and N2P2 components of both Aδ-fiber LEP (Aδ-LEP) and C-fiber LEP (C-LEP). All patients showed the N1P1 component of both Aδ-LEP and C-LEP. The Aδ-LEP N2P2 and C-LEP N2P2 components were present in 15 of 15 patients with MCS and 10 of 23 patients with VS/UWS (sensitivity for MCS 100%, 95% CI 78%–100%; specificity 57%, 95% CI 34%–77%; LR+ 2.30, 95% CI 1.44–3.67). Seven patients with VS/UWS showed neither Aδ-LEP N2P2 nor the C-LEP N2P2 (sensitivity for VS 30%, 95% CI 14%–53%; specificity 100%, 95% CI 75%–100%; LR+ with continuity correction 10.0, 95% CI 0.61–163.1).

A Class II study[e39] attempted to measure exogenous or endogenous attention as assessed by the P3a and P3b components of the P300 response occurring in response to a pair of word stimuli presented amongst distractors. Evidence of exogenous attention was identified in 1 of 9 patients with VS/UWS and 3 of 12 patients with MCS (sensitivity for MCS vs VS/UWS 25%, 95% CI 7%–57%; specificity 89%, 95% CI 51%–99%; LR+ 2.3, 95% CI 0.3–18.2). Evidence of endogenous attention was identified in 1 of 9 patients with VS/UWS and 0 of 12 patients with MCS (sensitivity for MCS vs VS/UWS 0%, 95% CI 0%–30%; specificity 89%, 95% CI 51%–99%; LR+ 0.26 with continuity correction, 95% CI 0.01–5.65).

Perturbational Complexity Index

Another Class I study[e34] evaluated the Perturbational Complexity Index (PCI), a measurement based on temporal and spatial quantification of EEG responses to transcranial magnetic stimulation (TMS). For this guideline, only the chronic cohort was considered, reflecting patients in VS/UWS or MCS (MCS+ or -) over 3 months after a traumatic, anoxic, or vascular insult. The study determined that the optimal PCI cutoff was 0.31 using a validation sample. Using this optimal PCI* cutoff, an index score greater than 0.31 had a sensitivity of 71% (95% CI 51%–86%) and a specificity of 96% (95% CI 80%–100%) for the diagnosis of MCS. LR+ was 3.375 (1.87–6.09).

Nasal cannula "sniff controller"

Another Class I study[e32] used a nasal cannula "sniff controller" connected to a transducer recording changes in nasal pressure and transforming these changes into an analyzable electrical signal. The breathing patterns of 25 patients with prolonged DoCs were measured at rest and in response to an instruction to sniff vigorously to end a music sequence. Eleven patients in VS/UWS and 14 patients in MCS were enrolled, with a positive response to command identified in 1 patient in MCS- (sensitivity of positive breathing test for MCS 7%, 95% CI 0.2%–22%; specificity 100%, 95% CI 68%–100%; LR+ using continuity correction 2.5, 95% CI 0.11–53.8).

Functional MRI

A Class II study[e36] enrolling 8 patients in VS/UWS and 16 patients in MCS (4 MCS-, 12 MCS+) used a word-counting task vs a control passive listening task while subjects underwent fMRI. A difference in activation between the 2 tasks was observed in 6/16 patients with MCS (6 MCS+, 0 MCS-) and 3/8 patients with VS (sensitivity for MCS 38%, 95% CI 15%–65%; specificity 63%,

96% CI 24%–91%; LR+ 1.00, 95% CI 0.33–2.99). However, the study notes that 7 patients had excessive movements precluding meaningful analysis (3 VS, 1 MCS-, 3 MCS+). When only those patients with interpretable findings were considered, 3/5 patients with VS and 6/12 patients with MCS showed differential activation (sensitivity for MCS 50%, 95% CI 21%–79%; specificity 40%, 95% CI 5%–85%; LR+ 0.83, 95% CI 0.33–2.08). Three of 8 patients diagnosed with VS/UWS due to absence of command-following on the Coma Recovery Scale-Revised (CRS-R) had the suggestion of high-level cognitive processing (37.5%, 95% CI 13.7%–69.4%).

One of the Class I EEG studies mentioned previously was Class II for fMRI data (due to < 80% of the cohort receiving fMRI).[e33] Twenty patients with either VS/UWS or MCS received fMRI testing using a motor imagery paradigm; 0/6 patients with VS/UWS and 3/14 patients with MCS had evidence of covert command-following with this testing. Evidence of covert command-following on fMRI was associated with a sensitivity of 21% for MCS (vs VS) (95% CI 6%–51%), specificity of 100% (95% CI 52%–100%), and an LR+ of 3.3 (using a continuity correction; 95% CI 0.2–55.0).

Another Class II study[e40] (for the comparison of MCS vs VS/UWS) enrolled 29 patients in VS/UWS and 26 patients in MCS and used fMRI blood oxygen level dependent (BOLD) signal to compare changes in brain activity in regions of interest elicited by presentation of factually correct and incorrect sentences. Of 29 patients with VS/UWS, 11 showed significant changes in activity in response to factually incorrect vs correct sentences (38%, 95% CI 23%–56%), and 5/26 patients in MCS demonstrated significant differences between conditions (19%, 95% CI 9%–38%). A positive response had 19% (95% CI 7%–40%) sensitivity and 62% (95% CI 42%–79%) specificity for MCS. The LR+ was 0.51 (95% CI 0.20–1.27).

Other imaging

One Class II study[e41] examined the use of structural MRI, resting state fMRI, and ^{18}F-fluorodeoxyglucose (FDG)-PET to assess default-mode network integrity for distinguishing between 72 patients in VS/UWS, 36 patients in MCS, and 11 patients with severe disability but no disturbance in consciousness. Injury to the default-mode network on imaging was assessed by blinded raters. Supplemental materials indicate that the presence of injury to the default-mode network on structural MRI was associated with increased odds of VS vs MCS (OR 2.84, 95% CI 1.58–5.11; AUC 0.72, 95% CI 0.62–0.81). Resting state fMRI could not differentiate between VS and MCS (OR 1.45, 95% CI 0.91–2.32; AUC 0.56, 95% CI 0.45–0.66). In the 85 patients who had FDG-PET, the presence of injury to the default-mode network on structural MRI was again associated with increased odds of VS vs MCS (OR 3.14, 95% CI 1.56–6.34; AUC 0.73, 95% CI 0.62–0.84) as was FDG-PET (OR 2.06, 95% CI 1.37–3.11; AUC 0.75, 95% CI 0.64–0.87) but not resting state fMRI (OR 1.54, 95% CI 0.89–2.68; AUC 0.57, 95% CI 0.45–0.69). Data were insufficient for calculating sensitivity, specificity, and LR+, and thus the approach used for assessing precision of the LR+ was applied to the diagnostic OR in formulating conclusions.

Conclusions

Electromyography

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 with decreased confidence in the evidence due to precision). There is insufficient evidence to support or refute the diagnostic value of the presence of EMG activity to command after adjusting for involuntary movements in distinguishing MCS from VS (LR+ 2.1, 95% CI 0.3–17.7) (very low confidence in the evidence, 1 Class I study with markedly decreased confidence in the evidence due to precision).

Electroencephalography

There is insufficient evidence to support or refute the diagnostic value of a finding of normal or mildly abnormal background on EEG in distinguishing patients with MCS from those with VS/UWS (LR+ 5.6, 95% CI 0.6–51.3 using a random-effects meta-analysis, I^2 = 57%) (very low confidence in the evidence based on 2 inconsistent Class I studies and a random-effects meta-analysis with poor precision, including the possibility of both important and unimportant effects). It is possible that EEG reactivity to at least 1 type of sensory stimulus distinguishes MCS from VS to a mildly important degree (low confidence in the evidence; 1 Class I study with decreased confidence in the evidence due to precision; LR+ 2.00, 95% CI 1.43–2.80). There is insufficient evidence to support or refute the diagnostic value of combining a low voltage background EEG pattern and the lack of EEG reactivity for distinguishing VS/UWS from MCS (very low confidence in the evidence, 1 Class I study with markedly decreased confidence in the evidence due to precision; LR+ 5.4, 95% CI 0.82–35.5). There is insufficient evidence to support or refute the use of specific entropy measures for distinguishing VS/UWS from MCS (very low confidence in the evidence, 1 Class III study with decreased confidence in the evidence due to precision of the ROC analysis).

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 with decreased confidence in the evidence due to precision; LR+ 2.30, 95% CI 1.43–3.67). There is insufficient evidence to support or refute the diagnostic value of the absence of Aδ-LEP N2P2 nor the C-LEP N2P2 components in response to LEPs for distinguishing VS/UWS from MCS (very low confidence in the evidence, 1 Class I study with markedly decreased confidence in the evidence due to precision; LR+ 10.0, 95% CI 0.61–163.1). There is insufficient evidence to support or refute the diagnostic value of evidence of exogenous or endogenous attention as assessed by the P3a and P3b components of the P300 response occurring in response to word stimuli for distinguishing MCS from VS/UWS (very low confidence in the evidence, 1 Class II study with markedly decreased confidence in the evidence due to precision; LR+ for exogenous attention 2.3, 95% CI 0.3–18.2, LR+ for endogenous attention 0.26, 95% CI 0.01–5.65).

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 with decreased confidence in the evidence due to precision; LR+ 3.375, 95% CI 1.87–6.09).

Nasal cannula "sniff controller"

There is insufficient evidence to support or refute the use of a nasal cannula "sniff controller" to distinguish MCS from VS (very low confidence in the evidence, 1 Class I study with markedly decreased confidence in the evidence due to precision; LR+ 2.4, 95% CI 0.11–53.8).

Functional MRI

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 with the LR+ suggesting no change in the probability of MCS with testing and CIs suggesting values of slight importance at most; LR+ 1.00, 95% CI 0.33–2.99). Results 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. There is insufficient evidence to support or refute the use of command-following on an fMRI motor imagery task to distinguish MCS from VS (LR+ 2.4, 95% CI 0.11–53.8) (very low confidence in the evidence, 1 Class II study with markedly decreased confidence in the evidence due to precision; LR+ 3.3, 95% CI 0.2–55.0). There is insufficient evidence to support or refute the use of an fMRI incorrect-minus-correct activation protocol to distinguish MCS from VS (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision; LR+ 0.51, 95% CI 0.20–1.27). Results were affected by the fact that 11 of 29 patients diagnosed with VS/UWS due to absence of command-following on the CRS-R had the suggestion of activation of language-related areas with the task (38%, 95% CI 23%–56%), the implications of which are uncertain. There is insufficient evidence to support or refute whether resting state fMRI is helpful in distinguishing between VS and MCS (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision, OR 1.45, 95% CI 0.91–2.32).

Other imaging

There is insufficient evidence to support or refute whether structural MRI (OR 2.84, 95% CI 1.58–5.11) or FDG-PET (OR 2.06, 95% CI 1.37–3.11) is helpful in distinguishing between VS and MCS (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision).

Natural history

For the natural history question, the guideline panel considered patients who were in VS/UWS or MCS for ≥ 28 days and for whom any consciousness-related outcome (i.e., frequency of death, VS/UWS, MCS, PTCS, severe disability, moderate disability, and good recovery) was measured at or near 3, 6, 12, 24, or > 24 months post injury. The guideline panel reviewed a total of 113 articles for the natural history questions and identified 18 meeting initial inclusion criteria.[e46-e63] After data extraction, it was determined that natural history is most appropriately investigated by stratifying patients separately by diagnosis and mechanism of injury, as these characteristics differentially affect the rate and degree of recovery (see prognosis section).[e64,e65] Although studies were required to have a minimum of 20 patients with prolonged DoC as determined by the inclusion criteria for the guideline, the guideline panel did not require subgroups to meet this criterion. Three studies[e49,e50,e54] did not analyze results separately for patients with specific diagnostic (VS/UWS or MCS) and etiologic (traumatic, nontraumatic) features. These studies are discussed below in a separate section to provide additional context, but no conclusions are drawn from these studies.

Natural history of patients with traumatic VS/UWS

For this population, 8 Class III studies were identified, reporting outcomes at 3 months, [e47,e55,e63] 6 months,[e47,e55,e63] 8 months,[e48] 12 months,[e47,e52,e53,e55,e63] and > 24 months[e56] post injury. Most of the studies are Class III because they enrolled patients from specialty rehabilitation programs, increasing the risk of bias for natural history estimates.

Three studies report outcomes at 3 months. One study[e63] found that by 3 months, 18 of 53 (34%, 95% CI 21%–47%) patients with traumatic VS/UWS recovered consciousness (emerged from VS/UWS). The second study[e47] reported that 16 of 34 patients (47%, 95% CI 31%–63%) recovered consciousness within 3 months. Recovery of consciousness occurred in 4 of 13 (31%, 95% CI 13%–58%) patients in the third study.[e55] A random-effects meta-analysis of these studies resulted in an estimated 38% of patients with traumatic VS/UWS transitioning to MCS within 3 months post injury (95% CI 29%–47%, $I^2 = 0$).

Three studies[e47,e55,e63] have data addressing the status of patients with traumatic VS/UWS at 6 months. The first showed that 35 of 53 (66%, 95% CI 53%–79%) transitioned from VS/UWS to MCS by 6 months. The second found that 8 additional patients in VS/UWS recovered consciousness between 3–6 months, in addition to the 16 who had recovered by 3 months, resulting in a total of 24 patients recovering consciousness within 6 months (24/34, 71%, 95% CI 54%–83%). The third study[e55] found that 4 additional patients in VS/UWS recovered consciousness between 3–6 months, in addition to the 4 who had recovered by 3 months, leading to a total of 8 patients recovering consciousness within 6 months (8/13, 62%, 95% CI 36%–82%). One of the 13 patients died before 6-month follow-up. When these 3 studies were assessed together, a random-effects meta-analysis found that 67% of patients with traumatic VS/UWS recovered consciousness by 6 months (95% CI 58%–76%, $I^2 = 0$).

Another study[e48] followed 19 patients who were in traumatic VS/UWS for an average of 2 months and assessed outcomes 6 months later at approximately 8 months post injury. By month eight, 16% (95% CI 0%–32%) died, 47% (95% CI 25%–70%) remained in VS/UWS, 21% (95%

CI 3%–39%) had partial disability on the Glasgow Outcome Scale–Extended (GOSE) (lower severe to lower good range), and 16% (95% CI 0%–32%) had full recovery (upper good range).

When all four 6- to 8-month studies were assessed together (noting that 3 are 6 months post injury and 1 is approximately 8 months post injury, with that study identifying 7 of 19 patients' recovery to at least partial disability on the GOSE), a random-effects meta-analysis found that 60% of patients with traumatic VS/UWS recovered to at least MCS by 6 to 8 months (95% CI 47%–74%, $I^2 = 62$).

Five studies considered 12-month outcomes for individuals with traumatic VS/UWS. One study[e47] found that 26 of 34 (76%; 95% CI 60%–87%) recovered consciousness by 12 months post injury, 2 of whom recovered between 6 and 12 months. Functional outcome ratings on the Disability Rating Scale (DRS) (see table e-1 for a description of the DRS) at 12 months revealed that 11.8% (95% CI 1%–22.6%) were in the extreme VS/UWS category, 11.8% (95% CI 1%–22.6%) were in the VS/UWS category, 41.2% (95% CI 24.6%–57.7%) were extremely severely disabled, 26.5% (95% CI 11.6%–41.3%) were severely disabled, 8.8% (95% CI 0%–18.4%) were moderate to severely disabled, and none achieved good recovery. Another study[e63] found that by 12 months, 28 of 35 patients with traumatic VS/UWS had recovered to MCS (80%, 95% CI 64%–90%). A third study[e55] reported that 10 of 13 patients with traumatic VS/UWS recovered to MCS by 12 months (77%, 95% CI 50%–92%), 1 of whom recovered between 6 and 12 months.

Two additional studies reporting 12-month outcomes[e52,e53] are confounded by the fact that they were conducted before the publication of the MCS definition and diagnostic criteria, so they may include individuals with MCS according to current standards. One of these studies retrospectively obtained Glasgow Outcome Scale (GOS) scores at 12 months post injury in 522 patients (male = 81%) between the ages of 3 and 83 years (median 30.5 years). At the 12-month follow-up, 19% (95% CI 16%–22%) had died, 20% (95% CI 16%–23%) remained in VS/UWS, 47% (95% CI 43%–51%) had severe disability, and 14% (95% CI 11%–17%) had moderate disability or good recovery, implying that 318 of 522 (61%, 95% CI 57%–65%) regained consciousness with variable degrees of residual disability.[e52] In the other study, recovery of consciousness was defined as the first occasion in which the patient was able to "establish a meaningful communicative contact with the environment by motor, visual or verbal act." By 12 months, 54% (95% CI 45%–62%) of the sample had recovered consciousness (mean time to recovery: 11.3 weeks, SD 8.9 weeks). Of those who remained in VS/UWS, 69% (95% CI 58%–81%) died within the first year (mean time to death 15.5 months, SD 21.6).[e52,e53]

A random-effects meta-analysis of the 3 more recent studies suggests that 78% of individuals in VS/UWS recover consciousness by 12 months (95% CI 69%–86%, $I^2 = 0$). In a random-effects meta-analysis of all 5 studies, 68% of individuals in VS/UWS recover consciousness by 12 months (95% CI 58%–77%, $I^2 = 76$).

Only 1 study[e56] looked at outcomes after 12 months in patients with traumatic VS/UWS. This study describes a cohort of 7 patients with traumatic VS/UWS, at least 5 of whom were living

more than 3 years after injury (71%, 95% CI 36%–92%). The other 2 patients were still alive at 1 month but had no follow-up data. Only survival was described in this study.

Conclusions

Thirty-eight percent (95% CI 29%–47%) of patients with traumatic VS/UWS possibly recover consciousness (emerge from VS/UWS) within 3 months post injury (low confidence in the evidence, 3 Class III studies). By 6 months post injury, 67% (95% CI 58%–76%) of patients with traumatic VS/UWS possibly recover consciousness (emerge from VS/UWS) (low confidence in the evidence, 3 Class III studies). When a separate study with 8-month results is included, the estimate is slightly lower: by 6–8 months post injury, 60% (95% CI 47%–74%) of patients possibly transition from VS/UWS to some degree of consciousness (low confidence in the evidence, 4 Class III studies). By 12 months, 68% (95% CI 58%–77%) to 78% (95% CI 69%–86%) of patients with a prolonged traumatic VS/UWS DoC possibly recover consciousness (low confidence in the evidence, multiple Class III studies). No identified studies specifically investigate the natural history of patients with traumatic VS/UWS after 12 months post injury (although some patients from this subgroup are included in mixed-population studies, as discussed below). There is insufficient evidence to draw conclusions regarding the frequency of other outcomes (e.g., degree of residual disability) (very low confidence in the evidence, only 1 Class III study reporting disability outcomes at 6 months and 2 Class III studies reporting disability outcomes at 12 months but using different scales, one of which was applied retrospectively in a potentially mixed VS/MCS cohort).

Natural history of patients with traumatic MCS

No study examined the natural history of patients in traumatic MCS in a manner that allowed outcome to be determined at specific time points for this subgroup.

Natural history of patients with nontraumatic VS/UWS

Four Class III studies reported outcomes in patients with nontraumatic VS/UWS.[e46,e48,e56,e62] Eighty-five percent (95% CI 77%–91%) of patients in nontraumatic VS/UWS were still living at 3 months in 1 study.[e46] In another study,[e56] at least 20 of 28 patients survived greater than 3 months (71%, 95% CI 53%–85%), with 2 patients dying at 3 months and the other 6 lost to additional follow-up; therefore, as many as 93% (95% CI 77%–98%) could have survived for more than 3 months. Using the conservative numbers (as death would be a common reason for loss to follow-up in this cohort), a random-effects meta-analysis of these 2 studies suggests 80% survival at 3 months (95% CI 67%–93%, $I^2 = 59$). No information on 3-month outcomes other than survival was identified.

In one of these studies, by 6 months, 20/100 (20%, 95% CI 12%–28%) of patients with nontraumatic VS/UWS had recovered consciousness,[e46] with recovery rates differing by etiology (cardiorespiratory disease 14.7%, stroke 20.6%, anesthesia 26.7%, encephalitis 12.5%, and other 33.3%). In another study[e62] where all patients had suffered anoxic injury, only 3 of 43 patients transitioned from VS/UWS to MCS by 7 months (7%, 95% CI 0%–15%). In a third study that

assessed outcomes at 6 months post enrollment (approximately 8 months post injury),[e48] 6 of 19 patients (32%, 95% CI 11%–53%) emerged from MCS with some persisting disability. When these studies were combined in a random-effects meta-analysis, the frequency of recovery of consciousness from VS/UWS with some degree of residual disability at 6–8 months post injury was 17% (95% CI 5%–30%, $I^2 = 76$).

When survival at 6 months was considered, 69 of 100 (69%, 95% CI 59%–77%) patients with nontraumatic VS/UWS were still living at 6 months in 1 study,[e46] although survival again differed by etiology and was lowest in those who had sustained cardiac arrest (10/34; 28.5%). In another study,[e56] at least 17 of 28 survived greater than 6 months (61%, 95% CI 42%–76%), but in the study investigating outcomes 6 months post enrollment and approximately 8 months post injury, only 8 of 19 were living at this time point (42%, 95% CI 23%–64%). With use of a random-effects meta-analysis and the more conservative estimates, 6- to 8-month survival of patients in nontraumatic VS/UWS is estimated at 60% (95% CI 45%–74%, $I^2 = 65$).

When considering longer duration outcomes (outcomes at 12 months or later), the study of patients in a prolonged anoxic vegetative state observed that of the 9 of 43 recovering consciousness (21%, 95% CI 11%–35%), 2 recovered between 3–6 months, 3 recovered at 6–12 months, and 4 recovered at 12–24 months, with the 2 individuals emerging from MCS falling in this later range (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).[e62] In the study of nontraumatic VS/UWS of mixed etiology where 20% of patients recovered consciousness before 6 months,[e46] no additional patients recovered consciousness after that time (0/80, 0%, 95% CI 0%–5%). Of the 80 patients who did not recover consciousness, 68 died within 72 months post injury, 5 were lost to follow-up after transfers to other medical facilities, and 7 remained alive at the time of last evaluation.[e46] In the study reporting only survival with substantial loss to follow-up,[e56] at least 12 of 28 survived greater than 12 months (43%, 95% CI 27%–61%; 3 known deaths, so survival could be as high as 25/28, 89%, 95% CI 73%–96%) and at least 8 of 28 survived over 24 months (29%, 95% CI 15%–47%); 4 known deaths, so survival could be as high as 24/28 (86%, 95% CI 69%–94%).

Two studies allowed calculation of the frequency of subsequent recovery of consciousness for patients remaining in nontraumatic VS/UWS at 6 months.[e46,e62] In the study of nontraumatic VS/UWS of mixed etiology discussed above,[e46] no patients recovered consciousness after 6 months (0/80, 0%, 95% CI 0%–5%). In the more recent study of prolonged anoxic VS/UWS, of 41 patients who remained in VS/UWS at 6 months, 7 patients recovered consciousness before 24 months (17%, 95% CI 9%–31%). When a random-effects meta-analysis of recovery between 6 and 24 months is performed in patients still in nontraumatic VS/UWS at 6 months, an estimated 7.5% may recover consciousness during this time (95% CI 0%–24%, $I^2 = 88$). However, it should be noted that these 2 studies were published 20 years apart (1993 and 2013), and there is high heterogeneity in the meta-analysis, likely reflecting factors such as different populations and advances in medical care between studies. Further studies are needed to determine whether the more recent study is a more accurate reflection of the current natural history of these patients.

Conclusions

It is possible that 3-month survival for patients with nontraumatic VS/UWS is 80% (95% CI 67%–93%, $I^2 = 59$) (low confidence in the evidence, 2 Class III studies). In this population, it is possible that 17% (95% CI 5%–30%) will recover consciousness (emerge from VS/UWS) at 6 months and 60% (95% CI 45%–74%) will survive to 6–8 months (low confidence in the evidence, 2 Class III studies for each conclusion). After 6 months in VS/UWS, it is possible that 7.5% may recover consciousness (emerge from VS/UWS) (95% CI 0%–24%) by 24 months (low confidence in the evidence, 2 Class III studies).

Natural history of patients with nontraumatic MCS

No study examined the natural history of patients in nontraumatic MCS in a manner that allowed outcome to be determined at specific time points for this subgroup.

Natural history of patients with different DoC diagnoses and pathophysiologic mechanisms of injury

Two Class II studies[e49,e50] and 1 Class III study[e54] that met inclusion criteria did not differentiate outcomes in patients with different diagnoses (i.e., VS/UWS and MCS) or pathophysiologic mechanisms (traumatic brain injury [TBI] and non-TBI).

Studies that stratified patients by DoC diagnosis but not pathophysiologic mechanism of injury

A Class III study investigating the long-term outcomes of patients with DoC (present for > 1 month and < 3 months) with and without epileptiform activity and seizures[e54] reported 30-month mortality rates in patients with VS/UWS (36.8%) and MCS (22.2%). Recovery rates were provided for patients with and patients without epileptic activity but not stratified by DoC diagnosis or mechanism of injury.

Outcomes were assessed at 2, 3, 4, and 5 years post injury in a Class II study that tracked recovery in 12 patients in VS/UWS and 39 in MCS with varied mechanisms of injury, all of whom were at least 1 year post injury at the time of enrollment.[e49] Among the VS/UWS subgroup, 36.4% died (95% CI 7.9–64.8) within 2 years, 45.5% (95% CI 16.0–74.9) within 3 years, 54.5% (95% CI 25.1–84.0) within 4 years, and 81.8% (95% CI 59.0–100) within 5 years. Of those still in VS/UWS at 2 years post injury, none recovered consciousness through the year 5 follow-up. In the MCS subgroup, 27.8% (95% CI 13.1–42.4) died within 3 years and 41.7% (95% CI 25.6–57.8) died within 5 years. No deaths occurred between years 4 and 5. Among survivors, 50.0% (95% CI 33.7–66.3) remained in MCS at 3 years, and, of those who emerged from MCS, 30.6% (95% CI 15.5–45.6) had severe disability on the GOS. At 4 years post injury, 27.8% (95% CI 13.1–42.4) were still in MCS and 36.1% (95% CI 20.4–51.8) had severe disability. At the 5-year follow-up, 25.0% (95% CI 10.9–39.1) were still in MCS, and none of those who were severely disabled at year 4 showed further functional improvement (3 cases were lost to follow-up).

Studies that stratified patients by mechanism of injury but not DoC diagnosis

The previously described Class III study investigating the long-term outcomes of patients with DoC (present for > 1 month and < 3 months) with and without epileptiform activity and seizures[e54] also reported 30-month mortality rates in people with VS/UWS or MCS from different mechanisms of injury. Mortality was 32.1% in patients with traumatic DoC, 23.7% in patients with DoC of vascular origin, and 43.2% in people with DoC of anoxic origin. Recovery rates were provided for patients with and patients without epileptic activity but not stratified by DoC diagnosis or mechanism of injury.

One Class II study grouped together patients in traumatic VS/UWS and MCS to form a DoC subgroup (n = 26) and compared outcomes in this subgroup with those in PTCS (n = 23) and those who had regained orientation (n = 38) at 4 weeks post injury.[e50] Outcome ratings were obtained between 3 and 8 years post injury (median = 62 months; range = 36–95 months) on the GOSE using a structured interview procedure with relatives and family members. All outcomes were assessed at or after 3 years post injury, but the specific length of time to assessment was not reported for each patient. For the DoC subgroup, 12.0% (95% CI 0%–24.7%) remained in VS/UWS, 52% (95% CI 32%–72%) were in the lower severe category of the GOSE, 4% (95% CI 0%–12%) were upper severe, 24% (95% CI 7%–41%) were lower moderate, and 4% (95% CI 0%–12%) were upper moderate. No patients were in the lower or upper good category.

Regarding productivity in a subgroup of 24 patients ages 7–64, none of the DoC subgroup returned to work or a mainstream academic curriculum, 17% (95% CI 2%–32%) returned to a modified academic schedule, 79% (95% CI 63%–95%) were disabled, and 4% (95% CI 0%–12%) had "other" outcomes.

Prognostic assessment

For the prognostic question, the guideline panel considered patients with traumatic VS/UWS or nontraumatic VS/UWS or MCS at least 28 days post injury and asked if any features or tests are helpful for prognosis. The 4 original prognostic questions (table e-2) specified features or tests of particular interest (profound thalamic injury, other lesion loci, grades of diffuse axonal injury (DAI), other biomarkers on structural imaging, functional neuroimaging, age at injury, sex, length of time post injury, injury mechanism, serial examinations, standardized behavioral examinations, electrophysiologic tests, or combination of factors). Outcomes of particular interest included permanent VS/UWS, recovery of consciousness (i.e., emergence from VS/UWS), emergence from MCS (EMCS), and degree of residual disability (i.e., severe, moderate, good recovery). EMCS and severe disability represent overlapping outcome categories; that is, all patients who meet minimum criteria for EMCS are in the disability category, but only some patients with severe disability meet the minimum criteria for EMCS. Consequently, studies vary as to how patients who meet minimum criteria for EMCS are categorized.

When reviewing the identified prognostic literature, 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 post injury. This approach was chosen because prognostic factors within each subgroup have more clinical relevance for individual patients and for the practicing provider. This plan was determined before evidence synthesis and was not based on the results of the systematic review, although the conclusions support this decision. Articles for which data could not be extracted to look at these subgroups were considered at the end, although their relevance to any particular subgroup is uncertain. For each prognostic factor, univariate analyses were considered. Predictive models with multivariable analyses were considered separately. For the prognostic questions, 266 articles were reviewed; 99 met initial inclusion criteria.

Prognostic value of diagnostic subtype (MCS vs VS/UWS)

Four Class II studies examined the prognostic value of diagnoses of MCS vs VS/UWS. One Class II study[e13] considered the prognostic value of MCS vs VS/UWS separately in patients with traumatic and nontraumatic DoC followed for 12 months. Diagnoses of MCS and VS/UWS were made on the basis of 2 consecutive assessments after admission to inpatient rehabilitation (9.2 ±4.5 weeks and 10.0 ±5.2 weeks post injury for the MCS and VS/UWS groups, respectively).

In an assessment of the odds of better than severe disability for patients in MCS compared with the odds for those in VS/UWS of traumatic etiology (n = 60), the OR was 13.75 (95% CI 3.9–48.3). For patients with a nontraumatic DoC (n = 25), MCS was associated with an OR for better than severe disability of 9.1 (95% CI 0.4–212.7).

The other 3 Class II studies investigated populations with mixed traumatic and nontraumatic etiologies. The first study focused on the outcome of emergence from MCS at 6 months. This study compared patients with MCS with patients with VS/UWS on admission to inpatient rehabilitation (144.9 ±81.6 days post injury, range 38–360 days). The OR for EMCS from MCS vs VS/UWS was 5.9 (95% CI 0.6–55.8).[e51] In the second study, which looked at the prognostic value of EEG, patients were enrolled upon admission to a rehabilitation unit and reexamined 6 months after the baseline EEG. The outcome of interest was "improvement," which for the VS/UWS group meant improving to MCS or better and for the MCS group meant any diagnosis better than MCS. In this study, patients with DoC were divided into 2 groups, those with and those without severe disturbances on EEG. When only those patients without a pathologic EEG (as defined by the study, n = 76: MCS = 38, VS/UWS = 38) were considered, there was no difference in outcome between MCS and VS/UWS (OR for "improvement" with MCS 1.0, 95% CI 0.28–3.57). When those patients with a pathologic EEG (n = 12) were included, the OR for improvement with MCS vs VS/UWS was 1.56 (95% CI 0.46–5.23).[e13] Finally, the third study looked at patients in DoCs of mixed etiology who had been in either VS/UWS or MCS for a year at study inclusion, and then followed these patients annually for 5 years. In this study, patients in VS/UWS vs those in MCS had an increased odds of functional deterioration on a modified version of the GOS that included a specific category for MCS (OR 3.37, 95% CI 1.28–8.87).[e49]

Many of these studies had limited precision; therefore, a logarithmic random-effects meta-analysis was performed. When the traumatic and nontraumatic populations in the first study were

combined,[e13] the combined OR for better than severe disability at 12 months in patients with MCS vs VS/UWS was 12.00 (95% CI 3.90–36.95). When this study was combined with the other 2 Class II studies looking at outcomes at 6–12 months, mixing traumatic and nontraumatic cohorts, a random-effects logarithmic meta-analysis resulted in an OR for improvement (generally defined, combining outcomes above) of 4.72 (95% CI 1.13–19.71, $I^2 = 66\%$) with a diagnosis of MCS vs VS/UWS.

Conclusions

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 with increased confidence in the evidence due to magnitude of effect). In prolonged DoC of nontraumatic origin, there is insufficient evidence to support or refute the prognostic value of an MCS diagnosis (as opposed to VS/UWS) for better than severe disability at 12 months (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision).

In patients with prolonged DoC of mixed etiology (traumatic and nontraumatic), a diagnosis of MCS is possibly associated with increased odds of improvement vs VS/UWS (OR 4.72, 95% CI 1.13–19.71, $I^2 = 66\%$) (low confidence in the evidence, meta-analysis of 3 Class II studies 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).

Prognostic value of traumatic vs nontraumatic injury

One Class I and 4 Class II studies examined the prognostic value of traumatic vs nontraumatic injury in patients with prolonged DoC.[e13,e49,e51,e65-e67]

One Class II study considered the prognostic value of etiology separately for patients with MCS vs VS/UWS.[e13] In the subgroup of 40 patients with MCS, a traumatic origin was associated with a significantly increased odds of better than severe disability at 12 months (OR 11.0, 95% CI 1.9–63.2). Only 2 patients in nontraumatic MCS had better than severe disability at 12 months, and both still had moderate to severe disability. In the subgroup of 45 patients with VS/UWS, the point estimate of the OR suggested increased odds of better than severe disability at 12 months with a traumatic etiology (OR 6.7, 95% CI 0.3–129.4), but this was not statistically significant.

Two Class II studies looked at traumatic vs nontraumatic injury as a univariate predictor in mixed populations of patients in MCS and patients in VS/UWS. In 1 study[e51] (n = 32) measuring emergence from MCS at 6 months after first study assessment, a traumatic etiology was associated with increased odds of emergence by point estimate (OR 5.0, 95% 0.8–30.2), but results were not statistically significant. In another Class II study[e67] mixing MCS and VS/UWS patients with an examination performed 1.2–127 months after insult, 6-month follow-up data were available for 46 of 90 (51%) of patients (excluding patients with prolonged DoC of

combined etiology and those with fat emboli or encephalitis). In the cohort with follow-up data, traumatic etiology was associated with increased odds of "improvement" (OR 5.5, 95% CI 1.2–24.3) vs nontraumatic injury. Improvement was defined differently for the different cohorts: for patients with VS/UWS, improvement was defined as MCS or better; for patients with MCS, it was defined as any diagnosis better than MCS, including the ability to communicate; and for patients already communicating, it was defined as a cognitive improvement as observed by 2 independent neuropsychologists.

Because of limited precision, a random-effects logarithmic meta-analysis was performed. Combining the raw data for the VS/UWS and MCS groups in the first study cited resulted in an OR of 9.41 (95% CI 2.03–43.53) for recovery of better than severe disability at 12 months in patients with a traumatic DoC.[e13] In a random-effects log meta-analysis combining the results of the 3 studies using mixed populations, DoC of traumatic etiology was associated with increased odds of improvement vs nontraumatic DoC (OR 6.52, 95% CI 2.59–16.43, $I^2 = 0$).

In a Class I study of 50 patients with DoC who were in VS/UWS for at least 6 months due to either traumatic or nontraumatic etiologies, etiology of the DoC was described as not impacting the proportion of "late recovery of responsiveness" where this was defined as > 12 months for patients with traumatic VS/UWS and > 3 months for patients with nontraumatic VS/UWS ($X^2 = 4.36$, df = 2, $p = 0.113$).[e65] Interpretation of these findings is difficult given different time considerations between groups. If considering recovery of consciousness during follow-up as an outcome, however, traumatic etiology was associated with greater odds of recovery (point estimate), although with wide CIs that include 1.0 (OR 5.9, 95% CI 1.0–33.7).

In a Class II study of patients with DoC who had already been in either VS/UWS or MCS for a year at study inclusion, the prognostic values of ischemic-anoxic encephalopathy and TBI were assessed.[e49] Patients with ischemic-anoxic encephalopathy DoC at 1 year had increased odds of deterioration in functional status by point estimate vs all other causes of coma, but the odds value was not statistically significant (OR for deterioration 2.69, 95% CI 0.88–8.22). Patients with TBI had increased odds of functional improvement by point estimate compared with all other causes of coma, but this odds value was again not statistically significant (OR 1.63, 95% CI 0.53–5.02).

Conclusions

In patients in prolonged MCS, a traumatic etiology, as opposed to a nontraumatic 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 with increased confidence in the evidence due to magnitude of effect). While point estimates favor a better prognosis with TBI vs nontraumatic injury in patients with prolonged VS/UWS, due to low precision, there is insufficient evidence to support or refute the prognostic value of TBI (vs non-TBI) in patients in VS/UWS for better than severe disability at 12 months (OR 6.7, 95% CI 0.3–129.4; very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision).

In mixed populations including patients with MCS and patients with VS/UWS, traumatic DoC, as opposed to a nontraumatic injury, is 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 [2 of which had sufficient precision on their own] combined in a meta-analysis with overall increased confidence in the evidence due to magnitude of effect).

There is insufficient evidence to support or refute the prognostic value of DoC etiology in patients with VS/UWS present for 6 months (OR 5.9, 95% CI 1.0–33.7; very low confidence in the evidence due to 1 Class I study with markedly decreased confidence in the evidence due to precision).

There is insufficient evidence to support or refute the prognostic value of ischemic-anoxic encephalopathy or TBI in patients with DoC present for 1 year (OR 1.63, 95% CI 0.53–5.02; very low confidence, 1 Class II study with decreased confidence in the evidence due to precision).

Patients with traumatic DoC

Prognostic factors for patients with traumatic VS/UWS

Eight studies[e13,e47,e53,e63,e68-e71] (2 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.[e53,e68,e72]

Age

Two Class II studies of patients with traumatic VS/UWS examined the prognostic value of age.[e47,e53] In a study of 34 patients assessed 2–3 months after injury and followed for 1 year,[e47] those patients who recovered consciousness by 12 months were an average of 6.2 years younger (-6.2 years, 95% CI -17.4 to 5.0; average age of group that recovered was 28.8 [SD 14.5] vs 35.0 [SD 14.0] in the group that did not recover). In a study of 148 patients with traumatic VS/UWS lasting over 30 days,[e53] patients who recovered consciousness were an average of 1.4 years younger (-1.4 years, 95% CI -6.38 to 3.58; average age 26.1 [SD 14.5] in the group that recovered and 27.5 [SD 14.8] in the group that did not recover). Ages were not dichotomized to allow calculation of an OR. When the 2 studies were combined in a random-effects meta-analysis, patients who recovered consciousness were 2.19 years younger (-2.19 years, 95% CI -6.7 to 2.4).

Gender

One of the Class II studies[e47] examined gender as a prognostic factor. In this study, there was essentially no difference in recovery between genders, but there was not sufficient precision to exclude an important effect of gender in either direction (OR for male gender for recovery 0.75, 95% CI 0.12–4.56).

Length of time post injury

Two studies[e13,e53] mention the prognostic value of length of time post injury, but both were rated Class IV for this outcome because measures of association could not be calculated.

Standardized behavioral assessment scores

One Class II study evaluated the prognostic value of standardized behavioral assessments. This study[e47] assessed the prognostic value of the DRS performed at study admission, 2–3 months post injury. A score of < 26 on DRS at study admission was associated with an OR of 30.67 for recovery (95% CI 2.52–373.56). Patients recovering consciousness at 12 months had an average 2.0-point lower score on the DRS at study admission vs the group that remained in a PVS (22.3 vs 24.3, mean difference -2.0, 95% CI -2.3 to -1.7). DRS scores at entry also correlated with nonrecovery at 1 year ($p < 0.01$, analysis not provided).

Neuroimaging results

One Class I study[e71] investigated the utility of BOLD signal in response to a familiar voice speaking the subject's name. The study enrolled a mixed population, but results were available by subgroup. Of 23 patients with traumatic VS/UWS, 12 of 13 patients with activation of higher order auditory association cortex improved to a "good" outcome (defined as MCS or EMCS) compared with 4 of 10 patients with no or significantly more limited activation (OR 18.0, 95% CI 2.2–162.7). Among those who improved, the length of time post injury at enrollment varied from 1 to greater than 12 months: < 3 months = 5, 3–6 months = 4, 7–12 months = 1 and > 12 months = 3. None of the 13 patients with traumatic VS/UWS who activated higher order auditory association cortex emerged from MCS (vs 1/10 patients with no or limited activation, OR 0 for EMCS with higher order activation, 95% CI 0–4.8).

One Class III study[e69] examined the prognostic value of brain SPECT scanning in patients with severe head injury who had been in VS/UWS for 1 month. SPECT was performed between 1 and 2 months post injury but was completed in only 28 of the 50 enrolled subjects. A normal SPECT scan (vs an abnormal SPECT with evidence of hypoperfusion) was associated with an OR of 58.3 (95% CI 2.8–1224.9) for a favorable outcome (defined as moderate disability or good recovery) at 1 year.

A Class II study[e70] examined the prognostic value of different MRI findings in 80 patients with closed-head injury in PVS at the time of the MRI performed 6–8 weeks post injury. The outcome assessed was remaining in PVS vs emerging to a non-PVS state by 1 year, with assessments performed at 2, 3, 6, 9, and 12 months post injury. Corpus callosum lesions were associated with an OR of 132.1 (95% CI 15.9–1100.7) for remaining in PVS. Dorsolateral upper brainstem injury was associated with an OR of 7.9 (95% CI 2.9–21.4) for remaining in PVS. Corona radiata injury on MRI performed 6–8 weeks after closed-head injury was associated with an OR of 3.7 (95% CI 1.5–9.6) for remaining in PVS.

Electrophysiologic test results

One Class II study[e47] examined the prognostic value of several electrophysiologic tests in 34 patients with posttraumatic VS/UWS acquired between 2–3 months post injury. The presence of P300 was associated with an OR of 114.14 (95% CI 5.32–2447.39) for recovery of consciousness within 12 months. A reactive EEG was associated with an OR of 19.0 (95% CI 1.97–83.4) for recovery within 12 months. The presence of somatosensory evoked potentials (SEPs) (normal or with reduced amplitude) was associated with an OR of 1.35 (95% CI 0.26–7.07) for recovery within 12 months, and the presence of brainstem auditory evoked responses (BAEPs) (normal or with increased I-IV interpeak latency [IPL]) was associated with an OR of 1.89 (95% CI 0.38–9.40) for recovery within 12 months.

Multivariable models or prediction rules for predicting recovery of consciousness

One Class II study[e47] examined multivariable models for prognostic factors in traumatic VS/UWS. In this study, a logistic regression model was developed to assess the utility of the DRS, EEG reactivity, and presence of P300 for recovery of consciousness. In this model, the presence of P300 was the only factor statistically associated with conscious recovery (OR 34.3; 95% CI 2.62–5.714 per the original article with a presumed typographical error; $p = 0.005$).

Given that the OR and CIs presented did not match, the CIs were recalculated using the OR and *p* value with the result of 95% CI 2.62–571.4. In this model, neither DRS (OR 2.25, 95% CI 0.14–37.2) nor EEG reactivity (OR 7.74, 95% CI 0.31–12.44) were associated with recovery of consciousness, but wide CIs include the possibility that these variables could be either positively or negatively predictive, and thus the study lacked precision to exclude an important prognostic value of these variables.

Other prognostic factors

Five Class II studies[e47,e53,e63,e69,e72] reported on the prognostic value of risk factors that were not separately specified as important a priori in the guideline questions; 2 of these studies[e53,e72] used the same cohort but approached it with different statistical methods and considerations and were considered together. Where measures of association were not provided for a specific prognostic feature, studies were considered Class IV with regard to that prognostic feature and those results are not further described.

One Class II study[e47] reported differences in clinical and demographic characteristics between patients in VS/UWS who did and did not recover consciousness (table e-3). The only feature with statistical significance was day-of-injury GCS score, but the lower CI was a difference of 0.05 and of no clinical relevance.

Two Class II studies[e53,e68] examined overlapping populations and were considered together. Of note, the number of patients in the cohort with information on any given prognostic feature varied widely (table e-3).

One Class III study[e69] evaluated the prognostic value of doll's eye movements, cold caloric testing, CT scan lesions, and diffuse axonal injury vs focal pathology on MRI. Significant *p* values were provided for doll's eye movements, the cold caloric test, and MRI findings, but confidence in this evidence was very low because this was a single Class III study with no reason identified for increased confidence.

One Class II study[e63] evaluated the prognostic utility of the Val66Met brain-derived neurotrophic factor (BDNF) polymorphism in patients with traumatic VS/UWS. This study found no prognostic utility of this polymorphism (OR for recovery of consciousness at 3 months with Met polymorphism 6/20 vs 12/33, OR 0.75, 95% CI 0.24–2.41; OR for recovery of consciousness at 6 months with Met polymorphism 14/20 vs 21/33, OR 1.33, 95% CI 0.42–4.28; OR for recovery of consciousness at 12 months with Met polymorphism 14/16 vs 14/20, OR 3.00, 95% CI 0.59–16.13), but CIs were too wide to exclude a potentially important effect.

Conclusions

In traumatic VS/UWS for at least a month:
The following factors are probably (moderate confidence in the evidence) associated with an increased chance of recovery of consciousness or improvement in degree of disability within 12 months:

- Higher level activation of the associated auditory cortex using BOLD fMRI in response to a familiar voice speaking the patient's name (OR 18.0, 95% CI 2.2–162.7) (moderate confidence in the evidence, 1 Class I study)
- DRS scores of < 26, 2–3 months post injury (OR 30.67, 95% CI 2.52–373.6) (1 Class II with increased confidence in the evidence due to magnitude of benefit)
- Detectable P300 at 2–3 months post injury (OR 114.1, 95% CI 5.3–2447.4) (1 Class II study with increased confidence in the evidence due to magnitude of effect)
- Reactive EEG at 2–3 months post injury (OR 19.0, 95% CI 1.97–183.4) (1 Class II study with increased confidence in the evidence due to magnitude of effect)

The following factors are possibly (low confidence in the evidence) associated with an increased chance of recovery of consciousness:

- Lower scores on the DRS in general 2–3 months post injury (recovery at 12 months, 1 Class II study)
- Normal SPECT scan (favorable outcome, OR 58.3, 95% CI 2.8–1224.9, 1 Class III study with increased confidence in the evidence due to magnitude of effect)
- The presence of P300 after controlling for DRS and EEG reactivity (recovery at 12 months, OR 34.3, 95% CI 2.62–571.4, 1 Class II study)

The following factors are probably (moderate confidence in the evidence) associated with a worse prognosis:

- Hydrocephalus in the late phase (OR 16.32 for failure to recover consciousness at 12 months, 95% CI 5.84–45.6 in one analysis and 8.1, 95% CI 3.6–17.9 in the other; 2 Class II studies using the same cohort and thus treated as a single Class II study, increased confidence due to magnitude of effect)

The following factors are possibly (low confidence in the evidence) associated with a worse prognosis:

- Corpus callosum lesions (OR 132.1, 95% CI 15.9–1100.7), dorsolateral upper brainstem injury (OR 7.9, 95% CI 9.2–21.4), or corona radiata injury (OR 3.7, 95% CI 1.5–9.6) on MRI performed 6–8 weeks post injury (1 Class III study, increased confidence due to magnitude of effect)
- Fever of central origin in the acute phase (OR 3.17 for failure to recover consciousness at 12 months, 95% CI 1.11–8.53, 1 Class II study)
- Diffuse body sweating in the acute phase (OR 6.2 for failure to recover consciousness at 12 months, 95% CI 1.6–24.0, 1 Class II study)
- Epilepsy in the late phase (OR 4.4 for failure to recover consciousness at 12 months, 95% CI 1.9–9.8, 1 Class II study)
- Respiratory disturbance (OR 2.7 for failure to recover consciousness at 12 months, 95% CI 1.2–5.9, 1 Class II study)
- Flaccidity in the acute phase (as opposed to decorticate or decerebrate posturing) (OR 6.0 for failure to recover consciousness at 12 months, 95% CI 1.7–21.0, 1 Class II study).

Age is possibly (low confidence in the evidence) not a prognostic factor (2 Class II studies with limited generalizability due to young average age).

There is insufficient evidence (very low confidence in the evidence) to support or refute the prognostic value of:

- Gender (1 Class II study with decreased confidence in the evidence due to precision)
- Presence of SEPs (normal or with reduced amplitude) at 2–3 months post injury (1 Class II study with decreased confidence in the evidence due to precision)
- BAEPs (normal or with increased I-IV IPL) at 2–3 months post injury (1 Class II study with decreased confidence in the evidence due to precision)
- DRS and EEG reactivity in a multivariable model also including P300 (1 Class II study with decreased confidence in the evidence due to precision; P300 was statistically significant in this model)
- Val66Met BDNF polymorphism (1 Class II study with decreased confidence in the evidence due to precision)
- Other risk factors (see text, insufficient evidence to support or refute based on studies with limited statistical precision).

Prognostic factors for patients with traumatic MCS

Only 1 study was identified involving this population. This Class I study[e71] described previously investigated the utility of BOLD signal in response to a familiar voice speaking the subject's name. Of the 19 patients with posttraumatic MCS, 8 of 16 with higher level activation had good recovery (EMCS) and 0 of 3 with lower level activation had good outcome (OR with continuity correction 6.0, 95% CI 0.43–72.53). There was insufficient evidence to support or refute a conclusion regarding use of this imaging in traumatic MCS given the wide confidence intervals

(very low confidence in the evidence, 1 Class I study with markedly decreased confidence in the evidence due to precision).

Prognostic factors for patients with traumatic DoC in populations where patients in VS/UWS and MCS are considered together

One Class II study[e73] examined multivariate predictor models in 124 patients in a traumatic DoC for at least 4–16 weeks after injury. When considering the outcome of DRS score at 16 weeks, later time at enrollment ($p < 0.001$), worse DRS score at enrollment ($p < 0.001$), and dantrolene use ($p = 0.11$) were associated with worse DRS score at 16 weeks; faster DRS change ($p < 0.001$) and amantadine use ($p < 0.005$) were each associated with better DRS score at 16 weeks when considered in different models (given a potential relationship between these variables). When considering the outcome of time until command-following, in the model using rate of DRS change (without medications), later time at enrollment ($p < 0.001$), worse DRS score at enrollment ($p < 0.001$), and left frontal lesions ($p < 0.001$) were all associated with later command following, while faster DRS change ($p < 0.001$) and left temporal lesions ($p < 0.008$) were associated with earlier command following. In the model including medications rather than rate of DRS change, later time at enrollment ($p < 0.001$), worse DRS score at enrollment ($p < 0.001$), and bilateral lesions ($p < 0.001$) were associated with later command following, and contusions/mass lesions ($p < 0.005$), subarachnoid hemorrhage ($p < 0.002$), and left temporal lesions ($p = 0.003$) were associated with earlier command following.

One Class III study[e74] studied the use of SEPs in patients with traumatic DoC who have DAI. SEPs were graded as normal (grade I) if N20 amplitude and central conduction time were normal, abnormal (grade II) if central conduction time was abnormally prolonged, or absent (grade III). With grade I SEPs, the sensitivity for favorable outcome (GOS 4–5) was 46% (95% CI 20%–74%), specificity was 97% (95% CI 81%–100%), and positive predictive value was 86% (95% CI 42%–99%). With grade III SEPs, the sensitivity for an unfavorable outcome (GOS 1–3) was 50% (95% CI 32%–68%), specificity was 100% (95% CI 72%–100%), and positive predictive value was 100% (75%–100%).

Conclusions

In patients with a traumatic DoC for at least 1 month, later time at enrollment, worse DRS score at enrollment, and dantrolene use are possibly associated with worse DRS score at 16 weeks, and faster DRS change and amantadine use are possibly associated with a better DRS score at 16 weeks in multivariable models (low confidence in the evidence, 1 Class II study). In patients with a traumatic DoC for at least 1 month, later time at enrollment, worse DRS score at enrollment, left frontal lesions, and bilateral lesions are possibly associated with a longer time to following first commands, and faster DRS change, left temporal lobe lesions, contusions/mass lesions, and subarachnoid hemorrhage are possibly associated with earlier command following in multivariable models (low confidence in the evidence, 1 Class II study). There is insufficient evidence to support or refute the use of SEPs in this mixed population (very low confidence in the evidence, 1 Class III study).

Patients with nontraumatic DoC

Prognostic factors for patients with nontraumatic VS/UWS

Two Class I studies[e62,e71] and 2 Class II studies examined prognostic factors for patients with nontraumatic VS/UWS.[e13,e46]

In a Class I study[e62] of 43 patients with post-anoxic VS/UWS, a logistic regression analysis found that CRS-R scores of ≥6 at study entry (more than 1 month after onset) (OR 4.61, 95% CI 1.05–11643.58) and the presence of SEPs (classified as present when N20 cortical response was recorded on at least 1 side) from bilateral median nerve stimulation recorded with standard procedures (OR 17.88, 95% CI 1.37–6511.41) were both independent predictors of recovery of responsiveness by 24 months post injury. Age ≤50 years (OR 0.96, 95% CI 0.65–1.06), DRS < 25 (OR 0.69, 95% CI 0.09–4.05), and the presence of paroxysmal sympathetic hyperactivity (OR 1.29, 95% CI 0.02–972.17) were not significant predictors in the logistic regression, but the CIs for these variables were wide.

In the Class I study[e71] described previously investigating the utility of BOLD signal in response to a familiar voice speaking the subject's name, 0 of 3 of the patients with nontraumatic VS/UWS and higher level activation had good outcomes, and 2 of 13 patients with no or lower order activation had good outcomes (OR 0.0, 95% CI 0.0–10.67). Only 1 patient achieved EMCS by 12 months (with activation of the primary auditory cortices; OR 0.0, 95% CI 0.0–27.8).

In a Class II study[e46] of 100 patients in nontraumatic VS/UWS for at least 1 month resulting from cardiorespiratory disease, stroke, anesthesia, encephalitis, or other causes, neither age ($r_{spearman}$ = -0.04, t = 0.41, DF = 98, $p > 0.1$) nor VS/UWS etiology ($X^2 = 7.61$, DF = 8, $p > 0.1$) were associated with recovery of consciousness in patients followed at least 72 months after onset, with low confidence in the evidence due to precision (limited ability to calculate precision with data for age and low precision for etiology). In the other Class II study,[e13] duration of VS/UWS since injury was the only variable assessed in this specific population. With a duration of VS/UWS of 3 months, 3 of 11 (27%, 95% CI 9.7%–56.6%) recovered consciousness at 12 months; with a duration of VS/UWS of 6 months, 1/10 (10%, 95% CI 1.8%–40.4%) recovered consciousness at 12 months, and with a VS/UWS duration > 6 months, 0/7 (0%, 95% CI 0%–35.4%) recovered consciousness at 12 months, but wide CIs limit interpretation.

Conclusions

In patients with nontraumatic VS/UWS, it is probable that CRS-R scores of ≥6 more than 1 month after onset (OR 4.61, 95% CI 1.05–11643.58) and the presence of SEPs (OR 17.88, 95% CI 1.37–6511.41) are important predictors of recovery of responsiveness by 24 months post injury (moderate confidence in the evidence, 1 Class I study). There is insufficient evidence to support or refute the prognostic significance of any other variables reviewed (very low confidence in the evidence, based on either Class I or Class II studies with decreased confidence in the evidence due to limited precision).

Prognostic factors for patients with nontraumatic MCS

Only 1 study was identified that included this population. This Class I study[e71] described previously investigated the utility of BOLD signal in response to a familiar voice speaking the subject's name. Of the 6 patients with nontraumatic MCS enrolled in this study, 1 of 4 with higher level activation recovered and 0 of 2 with lower level activation recovered (OR 1.33, 95% CI 0.055–28.9). There was insufficient evidence to support or refute a conclusion regarding use of this imaging in nontraumatic MCS given the wide CIs (very low confidence in the evidence, 1 Class I study with decreased confidence in the evidence due to precision/lack of statistical significance).

Prognostic factors in pediatric populations

We identified 2 Class II studies[e75,e76] evaluating prognostic factors in pediatric populations.

MCS vs VS/UWS

Only 1 Class II study[e75] examined the prognostic value of remaining in vegetative state vs recovery of consciousness with regard to mortality. While all 60 enrolled subjects were in PVS for at least 90 days, the study reported that children remaining in PVS were more likely to die than those children who became socially responsive ($p = 0.019$, no other numbers provided).

Traumatic vs nontraumatic etiology

Two Class II studies[e75,e76] examined the prognostic value of DoC of traumatic vs anoxic etiology. One study[e76] enrolling 127 children and adolescents in PVS found that traumatic (vs anoxic) etiology of the DoC was associated with increased odds of recovery at 3 months (OR 3.4, 95% CI 1.3–8.9), 6 months (OR 3.5, 95% CI 1.6–7.5), 9 months (OR 4.0, 95% CI 1.8–8.8), and 12 months (OR 4.3, 95% CI 1.9–9.6). Additionally, traumatic (vs anoxic) etiology was associated with increased odds of higher quality outcome as defined by a Barthel index value of 50 or more (OR 10.9, 95% CI 4.5–26.3).[e76] In the Class II study[e75] examining 60 children in PVS for greater than 90 days, subjects with traumatic (vs anoxic) injuries were reported to have better cognitive ($p = 0.001$) and motor ($p = 0.01$) outcomes (insufficient data to calculate ORs). Traumatic (vs anoxic) injury was also associated with increased odds of attaining the ability to take all feedings orally (OR 6.9, 95% CI 1.6–29.5).[e75]

Age

Neither study[e75,e76] found a statistically significant association between age and outcome; however, insufficient data were provided to calculate measures of effect.

Other prognostic factors

In 1 Class II study[e76] with 82 children and adolescents with traumatic VS/UWS, subjects with hyperthermia had worse quality of outcomes as measured by the Barthel index ($p < 0.01$), but

there were insufficient data to calculate an OR. Additionally, subjects with no posttraumatic autonomic dysfunction (e.g., posttraumatic hyperthermia, tachycardia, abnormal sweating, vomiting unrelated to feedings, and unintentional movements, compared with subjects who had one or more of these features) had a better chance of scoring higher than 50 on the Barthel index ($p = 0.01$, insufficient data to calculate OR).

Conclusions

In pediatric patients, traumatic (vs anoxic) etiology of PVS present for at least 30 days is possibly associated with increased odds of recovery at 3 months (OR 3.4, 95% CI 1.3–8.9), 6 months (OR 3.5, 95% CI 1.6–7.5), 9 months (OR 4.0, 95% CI 1.8–8.8), and 12 months (OR 4.3, 95% CI 1.9–9.6) (low confidence in the evidence, 1 Class II study). In pediatric patients with a DoC for at least 30 days, a traumatic etiology, as compared with an anoxic injury, is probably associated with a better quality outcome (defined as a Barthel index value of 50 or more) (OR 10.9, 95% CI 4.5–26.3) (moderate confidence in the evidence, 1 Class II study 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 (low confidence in the evidence, 1 Class II study). A traumatic etiology, as compared with an anoxic injury, is possibly associated with increased odds for taking all feedings orally (OR 6.9, 95% CI 1.6–29.5) (low confidence in the evidence, 1 Class II study).

In pediatric subjects with traumatic PVS for at least 30 days, the presence of hyperthermia at any time is possibly associated with worse quality of outcome as measured by the Barthel index (low confidence in the evidence, 1 Class II study). In subjects with traumatic PVS for at least 30 days, the absence of autonomic dysfunction, as compared with the presence of 1 or more features of autonomic dysfunction, is possibly associated with better quality of outcome as measured by the Barthel index (low confidence in the evidence, 1 Class II study).

There is insufficient evidence to support or refute the prognostic value of MCS vs VS/UWS in pediatric patients with PVS for at least 90 days (very low confidence in the evidence, 1 Class II study with confidence in the evidence downgraded for directness because all patients were in PVS at enrollment and the study only compared subsequent types of vegetative state).

Prognostic factors for mixed cohorts

Two Class I studies[e42,e48] and 7 Class II studies[e49,e51,e66,e67,e77-e79] examined prognostic factors in populations with mixed etiologies (traumatic vs nontraumatic) or mixed diagnoses (VS/UWS or MCS) or both in a way such that individual subgroups could not be distinguished. Evidence for mixed populations is considered here, again grouped by prognostic factor.

Age

Three Class II studies[e49,e51,e79] examined the prognostic importance of age in mixed populations. One Class II study[e51] examined the prognostic value of age (when dichotomized ≤33 vs > 33

years) in 32 individuals of mixed traumatic and nontraumatic causes in both VS/UWS and MCS (mean time since injury 144.9 ± 81.6 days, range 38–360 days). Older age (> 33 years) was associated with a point estimate suggesting lower odds of full recovery of consciousness, OR 0.2 (95% CI 0.03–1.1), but CIs were wide and crossed 1. A study including a mixed population of patients with VS/UWS and MCS of various etiologies assessed 18.5 ± 9.9 months after a baseline evaluation occurring 3.5 ± 2 months post injury used a composite outcome comprised of total CRS-R score plus points assigned for DoC subtype at last follow-up.[e79] Using a general linear model, the composite outcome score was significantly affected by patient age ($F_{1,21} = 5.30$, $p = 0.032$), where younger age was associated with better recovery. In a study of VS/UWS and patients in MCS of traumatic and nontraumatic etiology who had been in a DoC for at least a year,[e49] when age was dichotomized as < 39 vs ≥ 39 years, age ≥39 years was associated with an OR for deterioration in functional status of 2.58 (95% CI 2.58, 95% CI 1.03–6.45) and an OR for functional improvement of 0.71 (95% CI 0.22–2.26) (calculations were done with the same prognostic factor—age ≥39 years—for both deterioration and improvement).

Gender

The same 2 Class II studies that evaluated age also examined the prognostic importance of gender in mixed populations.[e49,e51] In the study enrolling patients with mixed etiologies in a DoC for 1–12 months, female gender was associated with OR for full recovery of consciousness of 0.67 (95% 0.11–4.1).[e51] In patients with a DoC for more than a year, male gender was evaluated as a prognostic factor for both improvement and deterioration in functional status. Male gender had OR of 1.52 (95% CI 0.58–3.97) for deterioration and an OR of 1.11 (0.35–3.57) for improvement.[49]

Length of time post injury

Two Class II studies evaluated the prognostic value of the length of time post injury. In 32 individuals of mixed traumatic and nontraumatic causes in both VS/UWS and MCS, when dichotomizing chronicity as ≤94 days vs > 94 days, duration of > 94 days was associated with a smaller chance of recovery (OR 0.09, 95% CI 0.01–0.6).[e51] When considered as a continuous variable, mean chronicity was 94 ± 36.4 days in the individuals who fully recovered consciousness and 161.8 ± 85.9 days in those who did not (mean difference -67.8, 95% CI -110.4 to -25.2).[e51] In a study of 88 patients with DoC of traumatic and nontraumatic origin (38 patients with VS/UWS without severe disturbance on EEG, 12 patients with VS/UWS with more pathologic resting EEG, and 38 patients in MCS) with only partial follow-up, patients who improved at follow-up tended to have a shorter disease duration (mean 3.5 months) compared with those who did not improve (mean 17.3 months) ($p = 0.054$, mean difference -13.8 months, 95% CI -27.8 to 0.2 months).[e67]

Level of education

One Class II study[e51] examined the prognostic value of level of education in a mixed population. In this study, level of education in the group that emerged from MCS was not different from the

that of the group that did not emerge (9.8 ± 3.0 vs 10.0 ± 3.9 years respectively; mean difference -0.2; 95% CI -2.8 to 2.4).

Standardized behavioral examinations

Three Class II studies[e49,e51,e79] evaluated the prognostic value of different standardized behavioral examinations in mixed DoC populations. In 32 individuals of mixed traumatic and nontraumatic causes in both VS/UWS and MCS, total CRS-R score at admission was associated with an OR of 5.9 (95% CI 0.6–55.8) for EMCS at follow-up (cut-point for dichotomization not stated).[51] In the same study, number of CRS-R subscales with scores above the cutoff for an MCS diagnosis were dichotomized (visual alone or visual + another subscale), and in the univariate analysis, number of subscales was associated with an OR of 2.4 (95% CI 0.9–6.3) for recovery.[e51] In a study using a composite outcome of CRS-R score plus points for DoC subtype at last follow-up,[e79] patients who were 3.5 ± 2 months post injury at baseline were reassessed 18.5 ± 9.9 months later. Higher composite scores at follow-up were associated with higher composite scores at baseline using a general linear model ($F_{1,21} = 7.17$, $p = 0.014$). In patients with DoC for more than a year, an initial GCS score of ≤4 (as compared with 5–8) was associated with an OR for functional deterioration of 2.51 (95% CI 0.86–7.35) and an OR for improvement of 1.62 (95% CI 0.53–5.02).[e49]

Functional neuroimaging

One Class II study[e77] investigated the prognostic utility of mental imagery fMRI in patients 4 weeks to 10 years after injury. Of 10 enrolled patients with VS/UWS of mixed etiologies, 5 patients with significant BOLD activation reached at least MCS during the observation period (at least 2 months), whereas 0 of 5 patients with VS/UWS without BOLD activation recovered to MCS (OR with continuity correction 100, 95% CI 3.6–2780.6). In 12 patients in MCS of various etiologies, 6/9 with evidence of activation emerged from MCS as opposed to 1/3 without activation (OR 4.0, 95% CI 0.34–42.0).

Electrophysiologic tests

EEG

Two Class I studies[e42,e48] and 3 Class II studies[e49,e54,e67] examined the prognostic value of different EEG paradigms and analyses. In a Class I study measuring approximate entropy (ApEn), a nonlinear EEG parameter,[e48] using cutoffs of ApEn ≥0.8 and < 0.8 and comparing outcomes of any recovery (MCS, Partial Recovery, Total Recovery) vs no recovery (VS/UWS, death), ApEn ≥0.8 was associated with an OR (with continuity correction) of 234.6 (95% CI 10.4–5287.5) favoring recovery. The other Class I study examined the prognostic value of automated mean resting state EEG entropy measurements and included 27 patients with a "chronic" DoC present for at least a month (10 individuals with VS/UWS and 17 individuals in MCS, both with DoC of mixed etiologies).[e42] In this population, there was no value of the test when analyzed using an ROC curve (AUC 0.5, 95% 0.3–0.8) but the 95% CI included potentially important values.

In a Class II study[e67] enrolling patients with PVS (divided into 2 groups, those with and without severe disturbances on EEG) and patients in MCS of varied etiologies, patients with mismatch negativity (MMN) on an EEG paradigm had higher odds of improvement 6 months after the baseline study than those where MMN was absent (OR 5.1, 95% CI 2.8–9.5). This remained true across subgroups ($p < 0.05$) and when adjusting for other variables ($p = 0.044$). This study also included other EEG paradigms and measures (N1-[P2], P3 [sine tones], P3 [complex tones], p3 [vowels], presence of at least one P3 response, P600 [semantic oddball], N400 [word-pairs], N400 [sentences], and at least 1 semantic response) but was Class IV in regard to these outcomes because no measures of association were calculable from the data provided.

Mismatch negativity on EEG performed "at the early stage of coma" was also evaluated in the Class II study enrolling patients with a DoC still present at 1 year.[e49] In this population, absence of MMN had an OR of 2.67 (95% CI 0.42–17.18) for functional deterioration and an OR of 0.57 (95% CI 0.14–2.31) for improvement.

While most articles utilizing EEG focused on particular paradigms, 1 Class II study simply evaluated the prognostic value of epileptiform activity and seizures (results for seizures discussed below) in patients with DoC (VS/UWS and MCS) of varied etiologies (traumatic, vascular, anoxic).[e54] The 130 patients enrolled were > 1 month and < 3 months post injury and followed for 6 months; outcome was assessed at 30 months post injury. Sporadic generalized epileptiform activity on EEG occurred in 2 patients with anoxic VS (2/45, 4.4%, 95% CI 1.2%–14.8%). Nongeneralized epileptiform activity was present in 48 of 130 patients (36.9% 95% CI 29.1%–45.5%), and periodic epileptiform patterns were observed in 11 of 130 patients (8.5%, 95% CI 4.8%–14.5%). For the 103 patients surviving the 6-month observational period, the presence of epileptic activity was not associated with increased mortality (20/55 patients with epileptiform activity died vs 14/48 without epileptiform activity; OR for death in the presence of epileptiform activity 1.4, 95% CI 0.6–3.1), but CIs included the possibility of an important effect in both directions. Similarly, the absence of epileptiform activity was not associated with a higher chance of recovery (21/48 of patients without epileptiform activity recovered vs 21/55 patients with epileptiform activity; OR for recovery in absence of epileptiform activity 1.3, 95% CI 0.6–2.7), but interpretation is limited by CIs that include the possibility of an important effect in both directions.

Brainstem evoked potentials/responses

The Class II study[e49] enrolling patients with a DoC still present at 1 year also examined the prognostic value of auditory N100 responses and BAEPs performed "at the early stage of coma." Absence of an auditory N100 response had an OR of 2.45 (0.71–8.41) for deterioration in functional status and an OR of 0.33 (0.10–1.04) for improvement. Abnormal BAEPs were associated with an OR of 2.38 (0.44–12.98) for deterioration and an OR of 0.64 (0.16–2.55) for improvement.

Middle latency auditory evoked potentials

The Class II study enrolling patients with a DoC still present at 1 year[e49] also examined the prognostic value of middle-latency auditory evoked potentials (MLAEPs) performed at an early stage of coma. Abnormal MLAEPs were associated with odds of 5.84 (1.75–19.44) for functional deterioration and odds of 0.36 (0.04–3.01) for improvement.

Polysomnography

In a study[e54] using a composite outcome of CRS-R score plus points for DoC subtype at last follow-up mentioned previously, patients who were 3.5 ± 2 months post injury at baseline were reassessed 18.5 ± 9.9 months later. Higher composite scores at follow-up were associated with the sleep-structure index score ($F_{3,21} = 9.43$, $p = 0.00038$), representing an association between increasing complexity of sleep architecture and a higher composite score at follow-up.

Multivariable models or prediction rules

Three Class II studies[e51,e66,e79] looked at combinations of prognostic factors and prediction models and rules. In the Class II study of 32 individuals of mixed traumatic and nontraumatic causes in both VS/UWS and MCS,[e51] a multivariate regression model including chronicity (dichotomized as ≤94 vs > 94 days), age (≤33 vs > 33 years), gender, etiology (traumatic vs nontraumatic), years of education, total CRS-R score at admission, initial status (VS/UWS vs MCS), and number of subscales with scores above the cutoff for a diagnosis of MCS (visual alone vs visual + other) was developed to predict emergence from MCS at follow-up. In this model, the only 2 factors for which ORs for emergence from MCS were provided were chronicity (OR 0.03, 95% CI 0.002–0.5) and number of CRS-R subscales scoring at MCS level (OR 3.4, 95% CI 0.8–13.4). All other characteristics were described as nonsignificant with no other information provided.

Another Class II study looked at the value of multivariable models including the Disorders of Consciousness Scale (DOCS) for the outcome of time to consciousness at 4, 8, and 12 months after injury.[e66] This study enrolled 113 individuals with traumatic and nontraumatic DoCs. Because of the large volume of data, only select results are presented here. In a model including baseline DOCS score (≤48 vs > 48), total change in DOCS score from first to last measurement (≤3 vs > 3), average DOCS score (≤51 or > 51), and etiology (traumatic vs nontraumatic), baseline DOCS was associated with increased odds of consciousness at 4 months (OR 8.67, 95% CI 1.84–40.87) but not 8 or 12 months. Traumatic etiology was associated with increased odds of recovery only for 8-month outcomes (OR 3.47, 95% CI 1.14–10.54). ORs for total change in DOCS and average DOCS scores were not significant. In another model including baseline DOCS score, change in DOCS score from first to second measurement (≤4 vs > 4), average DOC score, and etiology, the ORs for recovery of consciousness at 4 months were 7.01 (95% CI 1.21–40.60) for baseline DOCS, 1.08 (95% CI 1.00–1.17) for change in DOCS score, 1.19 (95% CI 1.06–1.34) for average DOCS score, and 3.11 (95% CI 0.81–11.92) for traumatic etiology. The OR associated with baseline DOCS score decreased to 0.90 (95% CI 0.74–1.08) at 8 months and 0.84 (95% CI 0.83–0.98) at 12 months. The average DOCS score remained predictive of recovery, with an OR of 1.38 (95% CI 1.11–1.72) at 8 months and 1.32 (95% CI 1.11–1.57) at 12 months; traumatic etiology also has a significant OR for recovery at 8 months (3.86, 95% CI

1.04–14.27). A third logistic regression model included baseline DOCS score, change in DOCS score between visits 1 and 3, average DOCS score, and etiology. In this model, only average DOCS score had an association with outcome (4 months: OR 1.24, 95% CI 1.01–1.53, 8 months: 1.27, 95% CI 1.03–1.58, 12 months: 1.35, 95% CI 1.07–1.69).

A third study used a general linear model with a composite outcome of CRS-R score plus points for DoC subtype at last follow-up, 8.5 ± 9.9 months after baseline.[e79] In patients with DoC of mixed etiology tested at 3.5 ± 2 months post injury, a model including sleep-structure index, baseline composite score, and age was highly significant ($F_{5,21} = 13.71$, $p < 0.00001$, adjusted $R^2 = 0.71$).

Other prognostic factors: absence of pupillary light response

The Class II study[e49] enrolling patients with a DoC still present at 1 year also examined the prognostic value of absence of the pupillary light reflex at an early stage of coma. Absence of a pupillary light reflex was associated with an OR of 2.91 (95% CI 0.92–9.22) for functional deterioration and an OR of 1.58 (95% CI 0.45–5.57) for improvement.

Other prognostic factors: epileptic seizures

One Class II study evaluated the prognostic value of epileptiform seizures in patients with DoC (VS/UWS and MCS) of varied etiologies (traumatic, vascular, anoxic).[e54] The 130 patients enrolled were > 1 month and < 3 months post injury and followed for 6 months; outcome was assessed at 30 months post injury. During the 6-month observational period, epileptic seizures occurred in 35 of 130 patients (26.9%, 95% CI 20.0%–35.1%), without significant differences identified based on DoC type (VS/UWS or MCS), etiology, or other potential confounders. Two-thirds of patients diagnosed with seizures were treated with antiepileptic drugs at study enrollment. In the 103 patients surviving the 6-month observational period, the presence of seizures was not associated with a higher 30-month mortality (8/33 patients with seizures died vs 26/70 without seizures, OR 0.5, 95% CI 0.2–1.4), nor was the absence of seizure associated with an increased chance of recovery at 30 months (31/70 patients without seizures recovered vs 11/33 with seizures, OR 1.6, 95% CI 0.7–3.7), though CIs for both calculations include the possibility of clinically important associations.

Multiple comorbidities

One Class II study[e78] investigated the prognostic utility of multiple comorbidities on 1-year functional independence measure (FIM) scores in patients with VS/UWS and MCS of mixed etiologies. After controlling for injury severity and type, having 3 or more complications during inpatient rehabilitation was an independent predictor of FIM scores at 1 year, with patients with 3 or more complications having an average 26 points lower FIM score (-26.2, 95% CI -46.3 to -6.1). This was judged to likely be clinically important even though the CIs include FIM scores of uncertain clinical significance.

Conclusions

Clinical predictors

In patients with VS/UWS or MCS of traumatic or nontraumatic etiology who have been in DoC for varying lengths of time (≥ 1 month), older age is possibly associated with a worse outcome (low confidence in the evidence, 3 Class II studies, 1 of which is consistent but lacks statistical precision, with decreased confidence in the evidence due to directness relating to variability in time post injury and time of outcome assessment). In patients with VS/UWS or MCS of traumatic or nontraumatic etiology who have been in the DoC for at least a year, an age greater than 38 years is possibly associated with higher odds of deterioration in functional status (OR for deterioration of 2.58, 95% CI 2.58, 95% CI 1.03–6.45; low confidence in the evidence, 1 Class II study). However, interpretation of this study is difficult given the mixed population and potential confounders. There is insufficient evidence to support or refute the prognostic value of gender in a mixed DoC population with a DoC present for 1–12 months (very low confidence in the evidence, 2 Class II studies with decreased confidence in the evidence due to lack of precision). Longer length of time post injury is possibly associated with a lower likelihood of functional improvement (low confidence in the evidence, 2 Class II studies, 1 of which has insufficient precision on its own). When dichotomizing time since injury as ≤94 days vs > 94 days, DoC of > 94 days is possibly associated with a lower likelihood of emergence from MCS at 6 months in a population with prolonged DoC (low confidence in the evidence, 1 Class II study). There is insufficient evidence to support or refute the prognostic value of level of education in a mixed DoC population (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision). In patients with DoC of varying origins, there is insufficient evidence to support or refute the use of the CRS-R to predict emergence from MCS at 6 months (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision). A higher baseline composite score combining the CRS-R score plus points for DoC subtype is possibly associated with a higher composite score at last follow-up 18.5 ± 9.9 months later in a mixed DoC population (low confidence in the evidence, 1 Class II study). In patients of mixed DoC (traumatic and nontraumatic) present for 1 year, there is insufficient evidence to support or refute the prognostic value of an initial GCS score (dichotomized as ≤4 vs 5–8) for functional deterioration or improvement (very low confidence in the evidence; 1 Class II study with decreased confidence in the evidence due to precision).[e49]

Neuroimaging

In patients with VS/UWS of mixed etiology, mental imagery fMRI possibly predicts recovery to MCS (OR with continuity correction 100, 95% CI 3.6–2780.6) (low confidence in the evidence based on 1 Class II study; not upgraded for magnitude of effect give small sample size and questions about generalizability). There is insufficient evidence to support or refute this technique in MCS of mixed etiology (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision).

Electrophysiologic measures

In patients with prolonged VS/UWS of mixed etiology, an ApEn value of ≥0.8 (vs < 0.8) is highly probably associated with increased odds of recovery of consciousness (emergence from VS/UWS) as assessed by the GOSE score at 6 months after the EEG (OR 234.6, 95% CI 10.4–5287.5) (high confidence in the evidence, 1 Class 1 study with increased confidence due to magnitude of effect). In patients with a DoC for at least 1 month (mixed etiology, both MCS and VS/UWS), the presence of MMN on EEG is probably associated with increased odds of improvement 6 months later (OR 5.1, 95% CI 2.8–9.5, moderate confidence in the evidence, 1 Class II study with increased confidence in the evidence due to magnitude of effect). In patients of mixed DoC (traumatic and nontraumatic) present for 1 year, abnormal early MLAEPs are possibly associated with an increased odds of deterioration in functional status over subsequent years (OR 5.84, 95% CI 1.75–19.44, low confidence in the evidence, 1 Class II study). In patients with a DoC for at least 1 month (mixed etiology, both MCS and VS/UWS), there is insufficient evidence to support or refute the prognostic value of automated mean resting state EEG entropy measurements (very low confidence in the evidence, 1 Class I study with no association found but with insufficient precision to exclude an important association). In patients with a DoC for > 1 month and < 3 months (mixed etiology, both MCS and VS/UWS), there is insufficient evidence to support or refute the value of epileptiform activity identified over 6-month follow-up for prognosis of 30-month outcomes (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to insufficient precision).

In patients of mixed DoC (TBI and non-TBI) present for 1 year, there is insufficient evidence to support or refute the prognostic value of the absence of MMN, the absence of an auditory N100 response, or abnormal BAEPs performed at an early stage of coma (very low confidence in the evidence, 1 Class II study with insufficient precision for improvement for each test). In patients with DoC of varying origins, increasing complexity of sleep architecture on polysomnography (PSG) performed 3.5 ± 2 months post injury is possibly associated with a higher composite outcome of CRS-R score plus points for DoC subtype assessed 18.5 ± 9.9 months after the PSG (low confidence in the evidence, 1 Class II study).

Multivariable models or prediction rules

Shorter DoC chronicity (≤94 days) is probably associated with increased odds of emergence from MCS at 6 months when controlling for age, gender, etiology, years of education, admission CRS-R score, initial DoC (VS/UWS vs MCS), and number of CRS-R subscale scores consistent with MCS-level behaviors (moderate confidence in the evidence, 1 Class II study with increased confidence in the evidence due to magnitude of effect). There is insufficient evidence to support or refute the prognostic value of the number of CRS-R subscales with scores indicating MCS in this model (OR 3.4, 95% CI 0.8–13.4; very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to lack of precision). Certain baseline and longitudinal DOCS scores are possibly associated with increased odds of recovery when controlling for other variables (low confidence in the evidence, 1 Class II study; see details of numerous analyses in systematic review). In patients with DoC of mixed etiology tested at 3.5 ± 2 months post injury, a model including sleep-structure index, baseline composite score, and age is possibly associated with a higher composite outcome of CRS-R score plus points for DoC subtype at follow-up 8.5 ± 9.9 months after testing (low confidence in the evidence, 1 Class II study).

Other prognostic factors

In patients of mixed DoC (traumatic and nontraumatic) present for 1 year, there is insufficient evidence to support or refute the prognostic value of the absence of a pupillary light reflex (very low confidence in the evidence, 1 Class II study with insufficient precision for improvement). In patients with DoC of varying etiologies (> 1 month and < 3 months post injury), there is insufficient evidence to support or refute the value of epileptic seizures identified over 6-month follow-up for the prognosis of 30-month outcomes (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to insufficient precision). The presence of 3 or more medical complications during inpatient rehabilitation is possibly associated with an increased risk of higher functional impairment 1 year after injury independent of injury severity or mechanism (low confidence in the evidence, 1 Class II study).

Therapeutic intervention

For the therapeutic question, we considered patients with traumatic VS/UWS or nontraumatic VS/UWS or MCS at least 28 days post injury and asked if any treatments (as compared with standard of care rehabilitation programs or custodial care) result in increased rates of recovery of consciousness or accelerated improvement on continuous measures of functional status. We also asked whether there are any prognostic factors identifying which patients will respond to these treatments.

One hundred and twenty-nine articles were reviewed for the therapeutic questions; 28 met inclusion criteria. Two were rated Class I[e80,e81] and 1 was rated Class III.[e82] Additionally, 1 therapy with Class IV evidence was associated with a Class III prognostic study predicting who might respond to the therapy.[e83,e84]

Treatment interventions intended to accelerate rate of recovery or improve functional outcome

One Class I RCT[e80] enrolled 184 individuals with either traumatic VS/UWS or traumatic MCS between 4 and 16 weeks post injury and randomized them to amantadine (doses 100–200 mg twice daily) vs placebo for 4 weeks. In the primary analysis, individuals receiving amantadine had a significantly faster recovery over 4 weeks in comparison with those individuals receiving placebo (difference in slope 0.24 [95% CI 0.07–0.4] points per week on the DRS, where lower scores indicate less disability). During the 2 weeks of washout following treatment, the improvement rate was significantly slower in those patients who had been treated with amantadine (difference in slope, 0.30 points per week, 95% CI 0.05–0.6). At 6 weeks, the DRS scores were similar between groups (estimated mean DRS scores [from figure 1 in the referenced publication] at 6 weeks 17.1 ± 4.7 in the amantadine group and 17.8 ± 4.9 in the placebo group; mean difference -0.7, 95% CI -2.1 to 0.7).[e80]

Differences between groups on secondary analyses often did not reach statistical significance. When using DRS categories as an outcome, amantadine was associated with an OR for moderate to severe disability (as opposed to severe disability or worse) of 1.7 (95% CI 0.8–3.5) and an OR

for vegetative state (as opposed to recovery from VS/UWS to at least extremely severe disability) of 0.48 (95% CI 0.24–0.96). When using the CRS-R and its 6 subscales (table e-1), point estimates favored a beneficial response with amantadine treatment but no results were statistically significant. The amantadine treatment effect size was similar regardless of diagnostic status (VS/UWS vs MCS) or time post injury at enrollment. There was no significant difference in the frequency of adverse events between groups.

Another Class I study evaluated the effectiveness of tilt table therapy with or without an integrated stepping device on level of consciousness, with the goal of enhancing arousal and communication abilities.[e81] Fifty participants in VS/UWS or MCS between 4 weeks and 6 months post injury following TBI, intracerebral hemorrhage or ischemic infarction after hypoxic brain injury were included. The primary outcome measure was the rate of improvement in the CRS-R after a 3-week treatment period consisting of ten 1-hour sessions over 6 weeks. Patients were randomized to either treatment with a conventional tilt table or treatment with a tilt table with an integrated robotic stepping device. They also received standard therapy services. Both groups improved at follow-up compared with baseline. When comparing median change CRS-R scores from baseline to follow up, conventional treatment was superior to the tilt table with the integrated robotic stepping device at 3 weeks (immediately posttreatment) (median [25%–75% percentile] for the stepping device group = 3 [0–5] vs conventional tilt table = 4 [3–8]; U-test; U = 144.5, z = -2.299 p = .021, r = -0.34) and 6 weeks (stepping device group = 4 [-1 to 6] vs conventional tilt table = 9 [5–10]; U-test; U = 122.0, z = -2.824, p = .005, r = -0.42).

One Class III study[e82] retrospectively investigated the effect of the multiple neurostimulants on recovery of consciousness and neurobehavioral function in 115 patients with prolonged DoC undergoing rehabilitation. Using the DOCS change score as the primary outcome, patients receiving 1 neurostimulant had a change of 4.12 (SD 12.69) and those receiving multiple neurostimulants had a change of 1.79 (SD 14.2), corresponding to a mean difference of -2.33 (95% CI -7.7 to 3.072). At 1-year post injury, 64% of individuals receiving multiple neurostimulants (54/84) and 57% of those receiving one neurostimulant (18/31) fully recovered consciousness, corresponding to an OR of 1.3 (95% CI 0.6–3.0) in favor of the multiple neurostimulant group. This single Class III study is insufficient to drive conclusions.

Only 1 study[e84] was identified that investigated whether certain prognostic features can predict who will respond to an intervention. This study investigated the value of electrophysiologic criteria for response to deep brain stimulation (DBS). For patients who received DBS, a positive electrophysiologic profile (using multiple measures) was associated with increased odds of recovery after DBS (8/10 vs 0/11 or 0.15/11.5, OR 88.0, 95% CI 5.4–1219.0). Additionally, for patients meeting electrophysiologic criteria, 8 of 10 who received DBS recovered and 0 of 6 who did not meet criteria recovered, associated with an OR of 48.0 using a continuity correction (95% CI 2.9–679.9). While the prognostic elements of this investigation were rated Class III, the study examining the value of DBS was rated Class IV for lack of a control group. The clinical importance of both studies is currently uncertain as both the Class IV therapeutic rating and Class III prognostic rating are insufficient to drive conclusions.

All other therapeutic articles identified either did not meet inclusion criteria (for example, including both patients with acute DoC and those with prolonged DoC in data analyses) or had substantial methodologic limitations.

Conclusions

Amantadine probably hastens functional recovery in patients with MCS or VS/UWS secondary to severe TBI over 4 weeks of treatment (moderate confidence in the evidence, 1 Class I study) and appears safe in this population. 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 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 (moderate confidence in the evidence based on 1 Class I study), but the benefit of tilt table treatment vs placebo/nontreatment is not established (no identified studies).

Prognostic factors associated with a differential response to treatment

There is insufficient evidence to support or refute a differential response to treatment based on the presence or absence of specific prognostic factors (very low confidence in the evidence, 1 Class III study investigating prognostic features for a therapy without evidence for use).

PUTTING THE EVIDENCE IN A CLINICAL CONTEXT

The results of this systematic review highlight important gaps in knowledge related to diagnosis, prognosis, natural history, and treatment interventions concerning patients with prolonged DoC. Some consistent weaknesses in study methodology were observed across studies, constraining the strength of the evidence. Among the weaknesses identified, small sample size was most prevalent, which limited study power and generalizability. Additionally, the number of studies available to inform the questions of interest was constrained by the criteria that were established a priori to qualify studies for inclusion. For example, the decision to include only studies that investigated individuals who were at least 28 days post injury disqualified many studies conducted in the acute care setting as well as those that either combined, or did not specify, the number of individuals above and below this threshold. Some well-designed studies in which the majority, but not all, of the individuals 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 some consistent trends in study design within each of the 4 areas that compromised the strength of the evidence.

Diagnostic assessment

The most important challenge related to validating more precise diagnostic approaches is the absence of a previously established reference standard with adequate sensitivity and specificity. The most commonly used reference standard (team consensus-based diagnosis) is associated

with a 30%–40% error rate. 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. This issue was commonly observed in studies investigating diagnostic applications of functional neuroimaging where the results of fMRI or PET studies were possibly consistent with conscious awareness, but the behaviorally based reference standard failed to detect any sign of consciousness. 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 a nonobjective measure. These 2 issues contributed heavily to the low level of evidence available to inform diagnostic recommendations.

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. This presents a problem for the clinician wishing to provide information about recovery to family members. 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 4–52 weeks post injury. Further limiting the strength of the evidence, studies often failed to stratify or subanalyze individuals by diagnostic subtype (VS/UWS vs MCS) and etiology (traumatic/nontraumatic), obscuring the trajectory of recovery. The fact that the majority of natural history studies enroll individuals at specialty rehabilitation centers is a further limitation, as the generalizability of 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 emergence from MCS or both, without attention to the corresponding level of disability. Importantly, studies that tracked functional outcome beyond 1 year suggest that 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.[e85,e86] 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 features known to be linked to outcome (e.g., diagnostic subtype, injury etiology, and length of time post injury), within-sample variability tended to be high along these dimensions, contributing to very 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 decision to discontinue life-sustaining care). This review has, however, identified some electrophysiologic, imaging, and behavioral procedures of which clinicians should be aware, as these procedures appear to inform prognosis in specific DoC subpopulations.

Therapeutic interventions

Guidelines for treatment of patients with prolonged DoC have not previously been established because of inadequacies in the existing evidence base. Although we identified 129 treatment studies, 101 were excluded because the intervention was studied during the acute phase of recovery (i.e., < 28 days post injury), there was no control group, or the study was not methodologically sound enough to drive treatment recommendations for other reasons.

Treatment effectiveness studies targeting patients with prolonged DoC 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 has been 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 sample size that is large enough to support a sufficiently powered treatment effectiveness study. Constraints on sample size also limit stratification of individuals 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 throughout the rehabilitation course apart from routine physical, occupational, and speech therapies. Clinicians should take note that amantadine is the only treatment that has been shown to advance the pace of recovery in patients with DoC. Surrogates should also be advised of the increased risk associated with interventions that lack evidentiary support.

PRACTICE RECOMMENDATIONS

Unless otherwise noted, all recommendations specifically apply to the population addressed in this guideline (individuals with prolonged DoC [i.e., ≥28 days]).

Recommendation 1

Rationale for recommendation 1

Our systematic review has highlighted the complexities of caring for patients with a prolonged DoC (i.e., ≥28 days) at every stage, including diagnosis, prognosis, and treatment. Such patients may be misdiagnosed due to confounding neurologic deficits[e20] or inexperience in examining

patients for subtle signs of consciousness.[e87] 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.[e88] In addition, patients with prolonged DoC frequently experience significant medical complications that can slow recovery and interfere with treatment interventions.[89] 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 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.[e90] 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.

Recommendation statement 1

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

Recommendation 2

Rationale for all of recommendation 2

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.[e91,e92] Underlying central and peripheral impairments such as aphasia, neuromuscular abnormalities, and sensory deficits may also mask conscious awareness.[e93-e95] Clinician reliance on nonstandardized procedures, even when the examination is performed by experienced clinicians, [e18-e20] contributes to diagnostic error, which consistently hovers around 40%. Diagnostic error also includes misdiagnosing the locked-in syndrome (a condition in which full consciousness is retained) for VS/UWS and MCS.[e96 e97] Accurate diagnosis of the level of consciousness is important because of its implications for prognosis and management.

Additional rationale for recommendation 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.[e18,e98] The validity and reliability of standardized neurobehavioral assessment scales for diagnosis of DoC subtype have been previously reviewed.[e22] Other techniques such as Individualized Quantitative Behavioral Assessment have been useful in distinguishing specific purposeful responses from generalized, nonpurposeful, or reflexive responses.[e99] 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 CRS-R,[e98] Wessex Head Injury Matrix,[e100] Sensory Modality Assessment and Rehabilitation Technique,[e101] Western NeuroSensory Stimulation Protocol,[e102] the DOCS,[e58] and the Sensory Stimulation Assessment Measure[e103] for use in clinical practice (with varying levels of confidence across measures).[e22]

Recommendation statement 2a

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

Additional rationale for recommendation 2b, serial evaluations

While there is insufficient high-quality evidence to recommend the use of serial evaluations to improve the diagnostic sensitivity and specificity among DoCs, 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 greater risk of misdiagnosis. Multiple behavioral evaluations over time may improve diagnostic reliability and accuracy as 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/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.

Recommendation statement 2b

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

Additional rationale for recommendation 2c, 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.

Recommendation statement 2c

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

Recommendation statement 2d

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

Additional rationale for recommendation 2e, 2f, use of multimodal evaluations

This systematic review identified that some electrophysiologic procedures (specifically, EMG thresholds for detecting response to motor commands, EEG reactivity, LEP responses, and the TMS-induced PCI) 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 (fMRI or PET) or routine EEG or evoked-response (ERP) studies as clinically useful adjuncts to behavioral evaluations to detect conscious awareness in patients diagnosed with VS/UWS. Additionally, functional imaging is not widely available and may not be clinically feasible in large numbers of patients. However, 2 reviewed studies[e36,e40] 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%, 95% CI 14%–69%, and 38%, 95% CI 23%–56%, 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 1 study of patients with VS/UWS based on standardized neurobehavioral assessment, functional neuroimaging studies (i.e., ^{18}F-FDG PET, active fMRI) performed at various times post injury (from < 1 month post insult to > 1 year post insult) demonstrated evidence of brain activity compatible with at least minimal conscious awareness in approximately 32% of patients scanned using ^{18}F-FDG PET or mental imagery MRI or both (13/41; 95% CI 20%–47%), with ^{18}F-FDG PET showing results consistent with MCS in 33% of patients diagnosed with VS/UWS by the

CRS-R (12/36, 95% CI 20%–50%) and mental imagery fMRI showing results consistent with MCS in 11% (3/28, 95% CI 4%–27%).[e44] 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%, 95% CI 24%–45%) were classified as suggestive of MCS, with a greater recovery of consciousness in those categorized as MCS than VS/UWS on the EEG (11/50 VS vs 11/23 MCS, with 2 lost to follow-up; risk difference 26%, 95% CI 3%–47%).[e104]

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 above), 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%) of cases.[e44]

Recommendation statement 2e

In situations where there is continued ambiguity regarding evidence of conscious awareness despite serial neurobehavioral assessments, or where confounds 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 net benefit).

Recommendation statement 2f

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

Recommendation 3

Rationale for recommendation 3

In patients with severe TBI, many of whom have a DoC, 1 study found that hospital mortality was 31.7% (95% CI 28.4%–35.2%), with 70.2% (95% CI 63.9%–75.7%) of those deaths associated with the withdrawal of life-sustaining therapy.[e88] 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 GCS motor score.[e88] While withdrawal of life-sustaining therapy in this TBI population was high, this systematic review identified that individuals with a DoC lasting longer than 1 month post injury may still attain functionally significant recovery after 1 year post injury. Additional research in populations overlapping those examined in the systematic review shows that patients with prolonged DoC can achieve at least some degree of functional independence during long-term follow-up. For example, 1 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 or more follow-up intervals (1, 2, and 5 years).[e85] 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% returned to school or work.[e86] While these studies examine 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.

Recommendation statement 3

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

*This is the 1 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 < 28 days from injury.

Recommendation 4

Rationale for recommendation 4

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,[e105] and 1 study suggests a 30% (95% CI 0%–55%) probability of observing behaviors suggestive of MCS in patients diagnosed with VS/UWS when assessments are conducted in the morning.[e91] 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.

Recommendation statement 4

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).

Recommendation 5

Rationale for recommendation 5

In patients diagnosed with traumatic VS/UWS for at least a month, DRS scores < 26 at 2–3 months post injury, a detectable P300 at 2–3 months post injury, a reactive EEG at 2–3 months post injury, and higher-level activation of the auditory association cortex using BOLD fMRI in response to a familiar voice speaking the patient's name (performed 1–60 months post insult) probably have prognostic utility, suggesting an increased chance of recovering consciousness within 12 months. In this population, a normal SPECT scan at 1–2 months post injury, lower DRS scores in general 2–3 months post injury, and a detectable P300 2–3 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 6–8 weeks post injury showing corpus callosal lesions, dorsolateral upper brainstem injury, or corona radiata injury are possibly associated with a worse prognosis (remaining in PVS) at 12 months. In patients diagnosed with nontraumatic VS/UWS, specifically post-anoxic VS/UWS, it is highly probable that CRS-R scores of ≥6 at study entry (more than 1 month after onset) and the presence of SEPs (classified as present when N20 cortical response was recorded on at least 1 side, performed 4.6 ± 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.

Recommendation statement 5 (posttraumatic VS/UWS)

Clinicians should perform the DRS at 2–3 months post injury (Level B) and may assess for the presence of P300 at 2–3 months post injury (Level C based on feasibility) or assess EEG reactivity at 2–3 months post injury (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 imaging 6–8 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 (Level B). Clinicians should perform a SPECT scan 1–2 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 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 speaking the patient's name to assist in prognostication regarding 12-month (post-scan) recovery of

consciousness for patients in traumatic VS/UWS 1–60 months post injury (Level C based on feasibility, cost).

Recommendation 6

Rationale for recommendation 6

In patients diagnosed with nontraumatic post-anoxic VS/UWS, it is highly probable that CRS-R scores of ≥6 obtained more than 1 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.

Recommendation statement 6 (nontraumatic, post-anoxic VS/UWS)

Clinicians should perform the CRS-R (Level B) and may assess SEPs (Level C based on feasibility) to assist in prognostication regarding recovery of consciousness at 24 months for patients in nontraumatic post-anoxic VS/UWS.

Recommendation 7

Rationale for recommendation 7

The 1994 AAN Multi-Society Task Force defined VS as "permanent" 3 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.[e2] 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.[e27] Relying only on the portion of the Task Force dataset that was extracted from the Traumatic Coma Data Bank[e106] (which appropriately defined VS and reported findings on 25 cases followed after 12 months), 6 patients (14%) recovered consciousness between 1 and 3 years post injury. 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 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 2, 3, 4, and 5 years post injury (1 lost to follow-up, 9 died, and 2 remained in VS/UWS), but due to the small sample size, CIs for the possibility of 1 improving were wide (0%, 95% CI 0%–24%).[e49]

When considering patients with nontraumatic VS/UWS for at least 1 month, recent studies suggest that some patients 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 (emerge from VS/UWS) at 6 months, and that after 6 months, it is possible that an estimated 7.5% (95% CI 0%–24%) may recover consciousness from nontraumatic VS/UWS. In 1 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, with the 2 individuals emerging from MCS falling in this later range (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). That is, of 41 patients who remained in VS/UWS at 6 months, 7 additional patients recovered consciousness before 24 months (17%, 95% CI 9%–31%).[e62] 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.

There is additional evidence suggesting that late transition to MCS from VS/UWS is not rare and may occur in as many as 20% of patients who meet the criteria for permanence. 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 (7 traumatic, 3 nontraumatic) recovered consciousness between 14 and 28 months post onset.[e65] 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 post onset, 8 (47.0%) regained this ability between 1 and 5 years post injury.[e85]

Although the majority of patients who remain in VS/UWS across the first 3 (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.[e107]

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. We suggest 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.

Recommendation statement 7

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

Recommendation 8

Rationale for recommendation 8

Evidence from the prognosis section of the systematic review 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.[e13] 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 above, evidence from the natural history section of the systematic review identified that individuals with a DoC at 1 month post injury may still attain functionally significant recovery after 1 year post injury, with additional longitudinal studies showing that approximately 20% of patients recover to the level where they could return to work or school.[e85,e86]

Recommendation statement 8

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

Recommendation 9

Rationale for recommendation 9

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.

Recommendation statement 9

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).

Recommendation 10

Rationale for recommendation 10

See rationale for recommendation 7.

Recommendation statement 10

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).

Recommendation 11

Rationale for recommendation 11

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.

Recommendation statement 11

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).

Recommendation 12

Rationale for recommendation 12

Complication rates are high in patients with prolonged DoC and negatively affect morbidity and mortality.[e78,e89,e108,e109] 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.[e107] Other, more severe, complications such as hydrocephalus, pneumonia, and paroxysmal sympathetic hyperactivity can disrupt rehabilitation efforts, as they often require rehospitalization.[e107] 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.[e107]

Recommendation statement 12

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

Recommendation 13

Rationale for recommendation 13

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.[e110,e111] Other studies suggest that the relationship between level of consciousness and pain perception is unclear.[e112,e113] 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.

Recommendation statement 13

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).

Recommendation 14

Rationale for recommendation 14

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.

Recommendation statement 14

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

Recommendation 15

Rationale for recommendation 15

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.

Recommendation statements 15

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

Recommendations concerning the pediatric population

Recommendation 16

Rationale for recommendation 16

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.

Recommendation statement 16

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).

Recommendation 17

Rationale for recommendation 17

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.

Recommendation statement 17

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).

Recommendation 18

Rationale for recommendation 18

No therapeutic studies identified for this systematic review enrolled pediatric populations, and the only therapeutic intervention shown to have efficacy in adults (aged 16–65 years) with DoC 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.

Recommendation statement 18

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. Our results have identified methodologic shortcomings that cut across most studies, as well as others that are specific to a particular type of study. In this

section, we provide recommendations that reflect lessons learned and should advance future research.

There are certain study design features that should be ubiquitous across all types of DoC studies. First, sample size must be adequate to answer the questions of interest. The larger the number of patients included, the less likely the results can be attributed to chance. The guideline panel found many studies with fewer than 20 individuals, rendering the studies underpowered and, thus, unable to show significant differences even when differences may have been present. Conversely, studies with very large sample sizes may have the statistical power to establish a difference, but the effect size may be small, limiting clinical meaningfulness. Prespecified statistical measures of precision (e.g., CIs) should be used to help ensure the results cannot be accounted for by chance. Studies should include a wide spectrum of patients. Including only patients that fall at a specific point along a disease continuum (e.g., MCS only vs all levels of consciousness) can exaggerate the diagnostic accuracy, prognostic sensitivity, and apparent degree of treatment effectiveness. Failure to adequately characterize the sample (e.g., injury mechanism, length of time post injury at enrollment) limits the clinical applicability of the results. One of the most prevalent design flaws encountered in this review was the failure to report or institute strategies to mitigate bias. To minimize risk of bias, examiners should be masked (e.g., investigator responsible for obtaining results of a novel diagnostic or prognostic test is unaware of whether the individual has the disease or risk factor), rater observations should be independent (e.g., investigator administering the intervention should be different than the one conducting the outcome evaluation) and the number of individuals who were untestable or lost to follow-up should be tracked.

To strengthen the existing evidence base supporting clinical management of patients with prolonged DoC, future research will need to adhere more closely to methodologic standards that have particular relevance to diagnostic, prognostic, natural history, and interventional questions.

Diagnosis

It is essential that an appropriate independent reference standard be selected to confirm or refute the accuracy of the diagnostic test used to identify the disease or outcome of interest. At a minimum, a consensus-based reference should be employed.

The percentage of individuals able to successfully undergo the diagnostic procedure should be at least 80%. Among functional neuroimaging studies, for example, completion rates have been estimated to be 50%–70%. Low completion rates can lead to faulty conclusions regarding the generalizability of the procedure across the range of patients who carry the diagnosis.

Diagnostic accuracy results should be reported using sensitivity and specificity values, likelihood ratios, and related probability measures.

Natural history

To minimize the influence of host factors when monitoring the natural history of a disease, cohorts should be stratified by diagnosis (e.g., VS vs MCS) and pathophysiologic mechanism (e.g., TBI vs stroke vs global hypoxia/anoxia). Grouping these characteristics often leads to wide CIs and limited interpretability of findings.

Many DoC natural history studies failed to establish a common temporal anchor for inclusion, resulting in high variability in patients' length of time post onset at enrollment. Follow-up intervals were frequently linked to date of admission, often making it impossible to determine the modal point at which individual milestones were attained. This problem can be avoided by directly yoking milestones to date of injury.

Specification of the setting(s) within which patients are recruited is important to mitigate selection biases that can impact natural history findings. For example, studies that recruit exclusively from private hospitals may inadvertently exclude patients with less favorable prognostic profiles.

Prognosis

As with data from natural history studies, prognostic data may be skewed by failing to account for subgroup differences related to different diagnostic and pathophysiologic features. Many DoC prognostic studies collapsed subgroup features that have been shown to contribute uniquely to explained variance in outcome (i.e., MCS and TBI > VS and non-TBI) into a single cohort.

The presence or absence of specific prognostic factors should be measured at specific time points. The temporal generalizability of some relatively strong predictors validated in acute settings (e.g., GCS score) is variable and may lose validity during the postacute and chronic phases. There is also a strong need to shift from reliance on univariate analyses to multivariable prediction models to account for important interactions between prognostic factors.

The results of prognostic accuracy studies should be reported using quantitative measures of association that gauge the relationship between the risk factor and selected outcomes. Appropriate prognostic metrics include positive and negative predictive values, relative risks, and proportional ORs.

Treatment

Treatment studies must take steps to control for a variety of factors that may lead to spurious conclusions regarding the effectiveness of the intervention on the target population. This requires use of a comparison or no-treatment control group.

Studies must demonstrate that patients assigned to different treatment arms were equivalent on baseline characteristics that may confound interpretation of the results. An example of an often-overlooked confounder in DoC treatment studies is the failure to account for spontaneous recovery, which continues across the first year post injury in some DoC subgroups. Randomized allocation (ensures patients have equal chance of assignment to treatment and control group) and

allocation concealment (prevents disclosure of treatment assignment) are effective strategies for mitigating bias in treatment studies.

Interventions should be well characterized in terms of nature of exposure, dose, and duration. Failure to adequately describe these aspects of the treatment may compromise generalizability and reproducibility.

The primary outcome measure must be valid, reliable, sufficiently granular, and clinically relevant. Many DoC treatment studies relied on crude measures (e.g., dichotomized GOS scores), which increase the likelihood that important treatment effects remain undetected while others focused on nonclinically relevant outcomes (e.g., magnitude of cortical activation on fMRI). There is clear need to develop more precise methods of assessing outcome. This can be accomplished by extending the floor and ceiling of existing functional outcome measures, or by employing a multidimensional battery of outcome measures that can home in on specific areas of function. Investigations funded by NIDILRR and the National Institute of Neurological Disorders and Stroke of the NIH to address these gaps are currently under way.

TABLES

Table e-1. Key definitions

Term	Definition
Coma	A state of complete unconsciousness in which there is no evidence of wakefulness (i.e., eyes remain continuously closed) or self or environmental awareness.
Vegetative state (VS), unresponsive wakefulness syndrome (UWS), post-coma unawareness (PC-U)	Spontaneous eye-opening signaling wakefulness, but no evidence of purposeful behavior suggesting awareness of self or environment.
Persistent vegetative state (PVS)	Diagnostic term that denotes a VS/UWS lasting more than 1 month following TBI or non-TBI.
Permanent vegetative state	Prognostic term applied 3 months after nontraumatic VS and 12 months after traumatic VS, indicating a high probability of irreversibility.
Minimally conscious state (MCS)	Condition of severely altered consciousness in which there is definite, but often subtle and inconsistent, behavioral evidence of self or environmental awareness.
MCS+	A subcategory of MCS defined by the presence of behavioral evidence of preserved receptive language function (e.g., command following, intelligible speech)
MCS-	A subcategory of MCS defined by the presence of nonlinguistic signs of conscious awareness (i.e., automatic movements, object manipulation, localizing limb or eye movements, visual fixation or pursuit, and affective behaviors that occur in relation to relevant environmental stimuli)
Emergence from MCS (EMCS)	Recovery of either reliable communicative behavior, which may occur through verbal (e.g., spoken or written yes/no responses) or gestural means (e.g., discernible yes/no head movements), or functional object use (i.e., the ability to demonstrate instrumental use of at least 2 different familiar objects).
Recovery of consciousness	Reemergence of reproducible behavioral evidence of at least 1 feature of MCS, signaling the transition from coma or VS/UWS to MCS.
Posttraumatic confusional state (PTCS)	A condition of altered consciousness occurring after a traumatic brain injury in which all of the following clinical features are present: impaired ability to focus, sustain and shift attention; impaired encoding and retrieval of recent experiences; impaired orientation to person, place, time, and/or situation; and symptom fluctuation (i.e., waxing and waning of the above features and their severities).

Locked-in syndrome	A neurologic syndrome characterized by tetraplegia, anarthria, and near-normal to normal cognition, primarily caused by a lesion involving the ventral pons. The loss of speech and motor function in the setting of spontaneous eyes opening can lead to misdiagnosis of VS/UWS.
Severe disability	A degree of cognitive and/or physical disability marked by dependence on others for self-care and activities of daily living.
Moderate disability	A degree of cognitive and/or physical disability marked by independence in the home and dependence on others when outside the home environment.
Mild disability	A degree of cognitive and/or physical disability that does not prevent independent functioning outside the home (including return to work or school) but may result in minor residual cognitive or physical deficits.
GOS/GOSE	A structured interview intended to measure disability and handicap resulting from acquired brain injury. Items address level of consciousness, actual or perceived ability to carry out basic self-care and activities of daily living, and level of independence in the home and community. The original GOS is divided into 3 categories: severe disability, moderate disability, and good recovery. The GOSE subdivides the upper three categories into an eight-category scale: dead, vegetative state, lower severe disability, upper severe disability, lower moderate disability, upper moderate disability, lower good recovery, and upper good recovery.
Disability Rating Scale	A structured interview intended to measure the degree of disability experienced by an individual with a history of TBI. The higher the total score, the greater the degree of disability. Questions pertain to neurologic function, self-care, and vocational activities. The first three items, "Eye Opening," "Communication Ability" and "Motor Response," are taken directly from the GCS. The next three items assess self-care (i.e., "Feeding," "Toileting" and "Grooming") and reflect the level of disability caused by cognitive (not physical) problems. The seventh item, "Level of Functioning," considers the level of assistance required for daily activities and is based on the combination of both cognitive and physical impairments. The eighth item, "Employability," reflects the respondent's judgment of the degree of assistance required to perform in the work setting, taking into account both cognitive and physical impairments.
Coma Recovery Scale–Revised	A standardized neurobehavioral assessment instrument designed to evaluate level of consciousness, establish

	prognosis, and monitor response to treatment in patients with DoC. Six hierarchically organized subscales measure auditory, visual, motor, oromotor/verbal, communication, and arousal functions mediated by brainstem, subcortical, and cortical networks. Results yield a total score, 6 subscale scores and a diagnostic impression. Administration and scoring guidelines are manualized, and key psychometric properties are well established.

Abbreviations: VS = vegetative state; unresponsive wakefulness syndrome = UWS; post-coma unawareness = PC-U; TBI = traumatic brain injury; MCS = minimally conscious state; EMCS = emergence from MCS; PTCS = posttraumatic confusional state; GOS = Glasgow Outcome Scale; GOSE = Glasgow Outcome Scale–Extended; GCS = Glasgow Coma Scale; DoC = disorders of consciousness.

Table e-2. PICO Questions for the Disorders of Consciousness Guideline

1. For patients with a prolonged (≥28 days) DoC after brain injury, do standardized behavioral assessment scales, individualized quantitative behavioral assessment protocols, structural or functional neuroimaging studies, electrophysiologic techniques, or nonstandardized bedside examination, as compared with either team consensus-based diagnosis or standardized assessment measures with high sensitivity and specificity, reliably detect recognizable signs of conscious awareness or specific DoC?
2. For patients with TBI who have disturbance in consciousness lasting at least 4 weeks, as compared with patients with non-TBI, what are the prevalence rates at 3, 6, 12, 24, and > 24 months post injury for (a) death, VS, MCS, and PTCS, and (b) severe disability, moderate disability, and good outcome?
3a, 3b. In patients with a prolonged (≥28 days) DoC after brain injury, are (a) serial evaluations, or (b) evaluation by expert vs less-experienced examiners, more sensitive and specific than team consensus-based diagnosis for distinguishing MCS from VS or MCS from PTCS? 3c. In patients with a prolonged (≥28 days) DoC after brain injury, are the Aspen behavioral criteria (i.e., 6/6 consecutively correct yes/no responses to basic orientation questions, or 2/2 appropriate responses to commands to demonstrate use of two different familiar objects), more sensitive and specific than team consensus in determining emergence from MCS?
4. In patients with a prolonged (≥28 days) DoC after brain injury, are functional imaging and electrophysiologic procedures, including PET, fMRI (passive and active paradigms), cognitive EPs, or qEEG, as compared with standardized behavioral evaluations that incorporate the Aspen diagnostic criteria, more sensitive and specific in distinguishing MCS from VS or MCS from PTCS?
5. Are patients in posttraumatic VS who have profound damage to the thalamus and thalamic connections, as compared with patients in VS without profound posttraumatic thalamic injury or with profound nontraumatic thalamic injury, more likely to develop permanent VS?
6. Are patients in posttraumatic VS at least 4 weeks post injury who have other lesion loci, high- vs low-grade diffuse axonal injury, or other biomarkers on structural imaging (i.e., CT, MRI, DTI), as compared with patients in posttraumatic VS without specified lesion loci,

grades of DAI, or other biomarkers on structural imaging, more likely to recover consciousness earlier?
7. For patients with either VS or MCS (due to traumatic or nontraumatic ABI) for at least 4 weeks, do the following favorable risk factors—age at injury onset younger than 40 years, female sex, length of time post injury < 3 months, traumatic injury mechanism, absence of profound bilateral injury to the thalamus and thalamic connections, emergence from VS within 30 days of injury onset, or a combination of the above—accurately identify those who will emerge from VS (for VS only), emerge from MCS, attain better than severe disability, recover the ability to communicate reliably through speech or gesture, recover the ability to independently perform basic self-care activities (e.g., eating, toileting, grooming), recover the ability to live independently, or recover the ability to return to work or school, compared with patients with the following unfavorable risk factors—age at injury onset older than 40 years, male sex, length of time post injury > 3 months, nontraumatic injury mechanism, presence of profound bilateral injury to the thalamus and thalamic connections, failure to emerge from VS within 30 days of injury onset, or a combination of the above?
8. For patients in VS and MCS at ≥4 weeks post injury, do serial examinations, standardized behavioral examinations, functional neuroimaging studies (passive and active paradigms), or electrophysiologic tests, as compared with a single examination or nonstandardized bedside examinations, predict recovery of consciousness or functional outcome on the DRS at 3, 6, and 12 months post injury better than assessments conducted at a single point in time?
9. For patients in VS or MCS (either traumatic or nontraumatic ABI) for at least 4 weeks post injury, do treatments, including pharmacologic agents, nutraceuticals, deep and surface electrical brain stimulation, hyperbaric oxygen, or structured sensory and environmental stimulation protocols, as compared with standard-of-care rehabilitation programs or custodial care, result in increased rates of recovery of consciousness (i.e., VS to MCS; MCS to emerged) or accelerated improvement on continuous measures of functional status[1] (either during treatment or long-term following treatment cessation)?
10. Are patients in VS and MCS at ≥4 weeks post injury exposed to the treatments listed in question 9 with characteristics including age at injury onset younger than 40 years, female sex, length of time post injury < 3 months, traumatic or nontraumatic injury mechanism, absence of profound bilateral injury to the thalamus and thalamic connections, emergence from VS within 30 days of injury onset, initial DRS or GOSE score, above-average (relative to norm) weekly rate of change on a functional outcome measure, or a combination of the above favorable risk factors, as compared with patients who lack the above characteristics (individually and in combination), more likely to have increased rates of recovery of consciousness (i.e., VS to MCS; MCS to emerged), accelerated rates of improvement on continuous measures of functional status[2] (either during treatment or long-term following treatment cessation), or better functional outcomes at 3, 6, 12, 24, and > 24 months post injury?

Abbreviations: DoC = disorder of consciousness; VS = vegetative state; MCS = minimally conscious state; PTCS = posttraumatic confusional state; EPs = evoked potentials; qEEG = quantitative EEG; DTI = diffuse traumatic injury; DAI = diffuse axonal inury; ABI = axonal brain injury; DRS = Disability Rating Scale; GOSE = Glasgow Outcome Scale–Extended.

Table e-3. Differences in clinical and demographic characteristics between patients in VS/UWS who did and did not recover consciousness

Prognostic feature	Finding
Increased ICP[e47]	Patients recovering consciousness had slightly *higher* odds of having experienced ICP > 25 (OR 1.33, 95% CI 0.22–8.10).
Day-of-injury GCS score[e47]	Score was 0.7 points higher in group that recovered consciousness, 95% CI 0.05–1.5.
Days of coma[e47]	Group that recovered consciousness had average 3.8 days *more* coma, 95% CI -8.2 to 15.8.
Days of sedation[e47]	Group that recovered consciousness had an average of 0.3 *more* days of sedation, 95% CI -4.1 to 4.7.
Days in the ICU[e47]	Group that recovered consciousness had an average 3.6 more days in the ICU, 95% CI -14.4 to 21.6.
Infection/sepsis[e47]	Patients recovering consciousness had lower odds of having experienced infection or sepsis, OR 0.22, 95% CI 0.04–1.18.
Craniotomy[e47]	Patients recovering consciousness had lower odds of having received a craniectomy (OR 0.9, 95% CI 0.14–5.68).
Shunting[e47]	Patients recovering consciousness had higher odds of having received shunting (OR 3.4, 95% CI 0.17–70.12).
Fever of central origin in the acute phase[e53]	Fever of central origin was associated with failure to recover consciousness (OR 3.167, 95% CI 1.105–8.531) (n = 75).
Diffuse body sweating in the acute phase[e53]	Diffuse body sweating was associated with nonrecovery of consciousness (OR 6.17, 95% CI 1.59–23.96) (n = 57).
Abnormal ADH secretion in the acute phase[e53,e72]	"Abnormal ADH secretion" was associated with nonrecovery (OR 3.14, 95% CI 1.02–9.62), but the CIs included ORs that are not clinically meaningful (n = 130). In the separate analysis using the same cohort, the OR point estimate for ADH dysfunction also suggested an association with nonrecovery of consciousness, but CI were wide and crossed 1 (OR 2.9, 95% CI 0.9–9.0).
Respiratory disturbance in the acute phase[e53,e72]	Respiratory disturbance was associated with an OR of 1.9 (95% CI 0.9–4.0) for nonrecovery of consciousness in the first analysis (although the *p* value in the reported analysis was reported to be $p < 0.04$) (n = 125). In the second analysis, ventilator disturbance was associated with an OR of 2.7 (95% CI 1.2–5.9) for nonrecovery.
Hydrocephalus in the late phase[e53,e72]	Hydrocephalus in the late phase was associated with OR of 16.32 for nonrecovery of consciousness (95% CI 5.84–45.60) (n = 105). In the second analysis, hydrocephalus was associated with an OR of 8.1 for nonrecovery (95% CI 3.6–17.9).
Presence of associated injuries[e53]	Presence of associated injuries was associated with OR of 2.26 (95% CI 0.11–4.61) for nonrecovery of consciousness.
Extraneural trauma[e72]	Extraneural trauma was associated with an OR of 1.9 (95% CI 0.9–3.9) for nonrecovery.

Early epilepsy alone (without later seizures)[e72]	Early epilepsy alone (without later seizures) was associated with an OR of 2.0 (95% CI 0.5–8.7) of nonrecovery.
Epilepsy in the late phase (after 1-week post injury)[e53,e72]	Epilepsy in late phase (was associated with an OR of 4.35 (95% CI 1.93–9.80) for nonrecovery of consciousness in the first analysis (n = 123). In the second analysis, when comparing late epilepsy with individuals with no seizures at all, the OR for nonrecovery was 2.5 (95% CI 1.0–6.0).
Motor reactivity in the acute phase[e53,e72]	Both studies excluded 4 patients described as having "normal" motor reactivity because the sample was so small; none of these patients had recovery of consciousness at 12 months. Of the remaining cohort, the first study identified motor reactivity as a significant predictor of outcomes ($p < 0.002$), but data were presented in a way that made calculating ORs difficult. In the second analysis, flaccidity on evaluation, as compared with either decorticate or decerebrate posturing, was associated with increased odds of nonrecovery (OR 6.0, 95% CI 1.7–21.0).

Abbreviations: VS/UWS = vegetative state/unresponsive wakefulness syndrome; ICP = intracranial pressure; OR = odds ratio; CI = confidence interval; GCS = Glasgow Coma Scale; ICU = intensive care unit; ADH = antidiuretic hormone.

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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 www.aan.com. For complete information on this process, access the 2011 AAN process manual, as amended (https://www.aan.com/Guidelines/Home/Development).

Appendix e-1. AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2. AAN GDDI members 2017–2019

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD; (Co-Vice-Chair); Stephen Ashwal, MD; Lori L. Billinghurst, MD; Brian Callaghan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Jeffrey Fletcher, MD; Gary S. Gronseth, MD (Senior Evidence-based Medicine Methodology Expert); Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Koto Ishida, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; Mia T. Minen, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Allison M. Pack, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Navdeep Sangha, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Eric J. Ashman, MD (Ex-Officio); Jacqueline French, MD (Ex-Officio, Guideline Process Historian)

Appendix e-3. ACRM committee members

ACRM Evidence and Practice Committee

A subgroup of ACRM Evidence and Practice Committee members and selected DOC subject matter experts without conflicts of interest reviewed the scientific quality and usability of the document.

Marcel Dijkers, PhD; Mark Johnston, PhD; Amy Shapiro, PhD; Yelena Goldin, PhD; David Anders, MS, CCC-SLP; Lisa Brenner, PhD

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Appendix e-4. NIDILRR Review Committee members

Ruth W. Brannon, MA, MSPH; A. Cate Miller, PhD

Appendix e-5. Complete search strategy

PVS MCS – Search Strategies

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TREATMENT
((((((unconsciousness[mh:noexp]) AND (brain injur*[tiab] OR TBI[tiab] OR TBIs[tiab] OR brain injuries[mh:noexp] OR head trauma*[tiab])) OR (Coma[mh:noexp] AND (("1990/01/01"[PDat] : "1994/12/31"[PDat]))) OR (consciousness disorders[mh:noexp] OR persistent vegetative state[mh] OR vegetative state*[tiab] OR consciousness disorder*[tiab] OR unawareness state*[tiab] OR disorders of consciousness[tiab] OR prolonged loss of consciousness[tiab] OR prolonged unconscious state*[tiab] OR minimally conscious state*[tiab] OR minimal conscious state*[tiab] OR posttraumatic confusion state*[tiab] OR posttraumatic confusional state*[tiab] OR post traumatic confusional state*[tiab] OR post traumatic confusion state*[tiab] OR prolonged posttraumatic unawareness[tiab]) AND (("1990/01/01"[PDat] : "2012/09/30"[PDat]))) NOT (advanced directive*[ti] OR advance directive*[ti] OR pope[ti] OR papal[ti] OR catholic*[ti] OR theolog*[ti] OR schiavo*[ti] OR quinlan*[ti] OR Cruzan*[ti] OR living will*[ti] OR Jewish[ti] OR Wanglie*[ti] OR Torah[ti] OR Talmud[ti] OR euthanasia[ti] OR assisted suicide[ti] OR right to die[ti] OR right to life[ti] OR assisted death[ti] OR Supreme Court*[ti] OR Christianity[ti] OR Muslim*[ti] OR Islam*[ti] OR moral[ti] OR morals[ti] OR morality[ti] OR John Paul II[ti] OR death with dignity[ti] OR legislation[ti] OR bioethicist*[ti] OR ethic*[ti] OR legal*[ti]) AND (Humans[Mesh] AND (Clinical Trial[ptyp] OR Letter[ptyp] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Case Reports[ptyp] OR Clinical Conference[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Congresses[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR Controlled Clinical Trial[ptyp] OR English Abstract[ptyp] OR Evaluation Studies[ptyp] OR Government Publications[ptyp] OR Guideline[ptyp] OR Historical Article[ptyp] OR Journal Article[ptyp] OR Multicenter Study[ptyp] OR Technical Report[ptyp] OR Validation Studies[ptyp]) AND ("1990/01/01"[PDat] : "2012/09/30"[PDat]))) OR (((((unconsciousness[mh:noexp]) AND (brain injur*[tiab] OR TBI[tiab] OR TBIs[tiab] OR brain injuries[mh:noexp] OR head trauma*[tiab])) OR (Coma[mh:noexp] AND (("1990/01/01"[PDat] : "1994/12/31"[PDat]))) OR (consciousness disorders[mh:noexp] OR persistent vegetative state[mh] OR vegetative state*[tiab] OR consciousness disorder*[tiab] OR unawareness state*[tiab] OR disorders of consciousness[tiab] OR prolonged loss of consciousness[tiab] OR prolonged unconscious state*[tiab] OR minimally conscious state*[tiab] OR minimal conscious state*[tiab] OR posttraumatic confusion state*[tiab] OR posttraumatic confusional state*[tiab] OR post traumatic confusional state*[tiab] OR post traumatic confusion state*[tiab] OR prolonged posttraumatic unawareness[tiab]) AND (("1990/01/01"[PDat] : "2012/09/30"[PDat])))

NOT (advanced directive*[ti] OR advance directive*[ti] OR pope[ti] OR papal[ti] OR catholic*[ti] OR theolog*[ti] OR schiavo*[ti] OR quinlan*[ti] OR Cruzan*[ti] OR living will*[ti] OR Jewish[ti] OR Wanglie*[ti] OR Torah[ti] OR Talmud[ti] OR euthanasia[ti] OR assisted suicide[ti] OR right to die[ti] OR right to life[ti] OR assisted death[ti] OR Supreme Court*[ti] OR Christianity[ti] OR Muslim*[ti] OR Islam*[ti] OR moral[ti] OR morals[ti] OR morality[ti] OR John Paul II[ti] OR death with dignity[ti] OR legislation[ti] OR bioethicist*[ti] OR ethic*[ti] OR legal*[ti]) AND (("1990/01/01"[PDat] : "2012/09/30"[PDat])) NOT medline[sb])) AND (stimulation[tw] OR sensory[tw] OR tape recording*[tw] OR audiotape*[tw] OR videotape*[tw] OR deprivation[tw] OR hyperbaric oxygen*[tiab] OR hyperbaric oxygenation[mh] OR treatment*[tw] OR treatment[sh] OR therapy[tw] OR therapies[tw] OR therapeutic*[tw] OR therapy[sh] OR bromocriptine[tw] OR lamotragine[tw] OR amitriptyline[tw] OR desipramine[tw] OR methylphenidate[tw] OR amantadine[tw] OR levodopa[tw] OR zolpidem[tw] OR baclofen[tw] OR dopamine agents[mh] OR dopaminergic drug*[tw] OR GABA agents[mh] OR gabaergic drug*[tw] OR drug therapy[mh] OR rehabilitat*[tw] OR rehabilitation[sh] OR dietary supplements[mh] OR dietary supplement*[tiab] OR neutraceutical*[tiab] OR pharmacologic*[tiab] OR range of motion exercise*[tiab] OR positioning[tiab] OR positional change*[tiab] OR postural[tiab] OR physical therapy modalities[mh] OR physical therapy[tiab] OR physiotherapy[tiab])) NOT ((((((((((((((((("Cambridge quarterly of healthcare ethics : CQ : the international journal of healthcare ethics committees"[Journal]) OR "Medical law review"[Journal]) OR "Medicine and law"[Journal]) OR "The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine & Ethics"[Journal]) OR "Kennedy Institute of Ethics journal"[Journal]) OR "The American journal of bioethics : AJOB"[Journal]) OR "The Journal of clinical ethics"[Journal]) OR "Journal of law and medicine"[Journal]) OR "Christian bioethics"[Journal]) OR "Nursing ethics"[Journal]) OR "Neuroethics"[Journal]) OR "The Hastings Center report"[Journal]) OR "Journal of Christian nursing : a quarterly publication of Nurses Christian Fellowship"[Journal]) OR "Bioethics"[Journal]) OR "Ethics & medicine : a Christian perspective on issues in bioethics"[Journal]) OR "Clinical ethics"[Journal]) OR "The national Catholic bioethics quarterly"[Journal]) OR "Journal of medical ethics"[Journal])

Embase
DIAGNOSIS
#25.8 AND #25.9
#25.9
Imaging*:de,ab,ti OR neuroimaging*:ab,ti OR diagnos*:de,lnk,ab,ti OR 'neuroradiology'/exp OR tomography:de,ab,ti OR 'pet scan':ab,ti OR 'pet scans':ab,ti OR spectroscopy:de,ab,ti OR mri:ab,ti OR mris:ab,ti OR fmri:ab,ti OR fmris:ab,ti OR 'neurologic examination'/exp OR 'evoked response'/exp OR 'evoked potential':ab,ti OR 'evoked potentials':ab,ti OR echoencephalography:de OR 'electroencephalography'/exp OR electroencephalography:ab,ti OR 'electroencephalogram'/exp OR electroencephalogram:ab,ti OR eeg:ab,ti OR eegs:ab,ti OR qeeg:ab,ti OR qeegs:ab,ti OR electromyleogra*:de,ab,ti OR emg:ab,ti OR emgs:ab,ti OR scale*:de,ab,ti OR 'clinical assessment tool':de OR measure*:de,ab,ti OR score*:de,ab,ti OR instrument*ti,ab OR index:de,ab,ti OR indices:de,ab,ti OR 'nuclear magnetic resonance'/exp OR 'nuclear magnetic resonance':ab,ti OR 'cognitive ep':ab,ti OR 'cognitive eps':ab,ti OR 'event related potential'/exp OR 'event related potential':ab,ti OR 'event related potentials':ab,ti OR

spect:ab,ti OR spects:ab,ti OR 'ct scan':ab,ti OR 'ct scans':ab,ti OR 'ct x-ray':ab,ti OR 'ct x-rays':ab,ti OR 'cine-ct':ab,ti OR tomodensitometry:ab,ti OR radiodensitometry:de,ab,ti OR 'sensory modality assessment':ab,ti OR 'sensory modality assessments':ab,ti OR 'sensory stimulation assessment':ab,ti OR 'wessex head injury matrix':ab,ti OR 'western neuro sensory stimulation profile':ab,ti OR 'sensitivity and specificity':de OR specificity:ab,ti OR 'predictive value':de,ab,ti OR 'predictive near/3 value':ab,ti OR 'confidence interval':de OR detect*:ab,ti OR characteristic*:ab,ti OR command*:ab,ti OR categoriz*:ab,ti OR categoris*:ab,ti OR distinguish*:ab,ti OR differentiat*:ab,ti OR 'behavioral assessment':ab,ti OR 'behavioral assessments':ab,ti OR 'behavioural assessment':ab,ti OR 'behavioural assessments':ab,ti OR 'behavior assessment':ab,ti OR 'behaviour assessment':ab,ti OR 'behaviour assessments':ab,ti AND [1990-2012]/py
#25.8
#25.6 NOT #25.7
#25.7
'advanced directive':ti OR 'advanced directives':ti OR 'advance directive':ti OR 'advance directives':ti OR pope:ti OR papal:ti OR catholic*:ti OR theolog*:ti OR schiavo*:ti OR quinlan*:ti OR cruzan*:ti OR 'living will':ti OR 'living wills':ti OR jewish:ti OR wanglie*:ti OR torah:ti OR talmud:ti OR euthanasia:ti OR 'assisted suicide':ti OR 'right to die':ti OR 'right to life':ti OR 'assisted death':ti OR 'supreme court':ti OR christianity:ti OR muslim*:ti OR islam*:ti OR moral:ti OR morals:ti OR morality:ti OR 'john paul ii':ti OR 'death with dignity':ti OR legislation:ti OR bioethicist*:ti OR ethic*:ti OR legal*:ti AND [1990-2012]/py
#25.6
#25.5 AND ('article'/it OR 'article in press'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) AND ('case report'/de OR 'case study'/de OR 'clinical article'/de OR 'clinical protocol'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'human'/de OR 'human tissue'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'methodology'/de OR 'model'/de OR 'multicenter study'/de OR 'normal human'/de OR 'outcomes research'/de OR 'practice guideline'/de OR 'prospective study'/de OR 'questionnaire'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de)
#25.5
#25.1 OR #25.2 OR #25.3 OR #25.4
#25.4
unconsciousness:de AND ('head injury'/exp OR tbi:ab,ti OR tbis:ab,ti OR 'brain injury':ab,ti OR 'brain injuries':ab,ti OR 'brain injured':ab,ti OR posttraumatic:ab,ti OR 'post-traumatic':ab,ti) AND [embase]/lim AND [1990-2012]/py
#25.3
'consciousness disorder':de OR 'consciousness disorder':ab,ti OR 'consciousness disorders':ab,ti OR 'disorders of consciousness':ab,ti AND [embase]/lim AND [1990-2012]/py
#25.2
'persistent vegetative state':de OR 'minimally conscious state':de OR 'vegetative state':ab,ti OR 'vegetative states':ab,ti OR 'minimal conscious state':ab,ti OR 'minimal conscious states':ab,ti OR 'minimally conscious state':ab,ti OR 'minimally conscious states':ab,ti OR 'unawareness state':ab,ti OR 'unawareness states':ab,ti OR 'posttraumatic confusional state':ab,ti OR ‘post-

traumatic confusional state’:ab,ti OR ‘posttraumatic confusion state’:ab,ti OR ‘post-traumatic confusion state’:ab,ti OR 'posttraumatic confusional states':ab,ti OR ‘post-traumatic confusional stateS’:ab,ti OR ‘posttraumatic confusion states’:ab,ti OR ‘post-traumatic confusion states’ OR 'prolonged posttraumatic unawareness':ab,ti OR 'prolonged post traumatic unawareness':ab,ti OR 'prolonged unconscious state':ab,ti OR 'prolonged loss of consciousness':ab,ti AND [1990-2012]/py
#25.1
'coma'/exp AND [embase]/lim AND [1990-1992]/py

Embase
PROGNOSIS
#24.10
#24.8 AND #24.9
#24.9
convalescence:de,ab,ti OR convalesce:ab,ti OR convalesces:ab,ti OR convalesced:ab,ti OR convalescing:ab,ti OR 'disease course':de,ab,ti OR 'adverse outcome':de,ab,ti OR deteriorat*:de,ab,ti OR 'disease duration':de,ab,ti OR 'disease exacerbation':de,ab,ti OR 'general condition deterioration':de OR 'general condition improvement':de OR improve*:ab,ti OR improving:ab,ti OR 'illness trajectory':de OR prognos*:de,ab,ti OR 'disease free survival':de,ab,ti OR predict*:de,ab,ti OR recover*:de,ab,ti OR 'functional level':ab,ti OR emerge:ab,ti OR emerges:ab,ti OR emergence:ab,ti OR emerged:ab,ti OR emerging:ab,ti OR restoration:ab,ti OR restore*:ab,ti OR outcome*:de,ab,ti OR 'recovery of function':ab,ti OR 'follow up':de OR recuperat*:ab,ti OR 'treatment failure'/exp OR 'treatment failure':ab,ti OR nomogram*:de,ab,ti OR progress:ab,ti OR progresses:ab,ti OR progressed:ab,ti AND [1990-2012]/py
#24.8
#24.6 NOT #24.7
#24.7
'advanced directive':ti OR 'advanced directives':ti OR 'advance directive':ti OR 'advance directives':ti OR pope:ti OR papal:ti OR catholic*:ti OR theolog*:ti OR schiavo*:ti OR quinlan*:ti OR cruzan*:ti OR 'living will':ti OR 'living wills':ti OR jewish:ti OR wanglie*:ti OR torah:ti OR talmud:ti OR euthanasia:ti OR 'assisted suicide':ti OR 'right to die':ti OR 'right to life':ti OR 'assisted death':ti OR 'supreme court':ti OR christianity:ti OR muslim*:ti OR islam*:ti OR moral:ti OR morals:ti OR morality:ti OR 'john paul ii':ti OR 'death with dignity':ti OR legislation:ti OR bioethicist*:ti OR ethic*:ti OR legal*:ti AND [1990-2012]/py
#24.6
#24.5 AND ('article'/it OR 'article in press'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) AND ('case report'/de OR 'case study'/de OR 'clinical article'/de OR 'clinical protocol'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'human'/de OR 'human tissue'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'methodology'/de OR 'model'/de OR 'multicenter study'/de OR 'normal human'/de OR 'outcomes research'/de OR 'practice guideline'/de OR 'prospective study'/de OR 'questionnaire'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de)
#24.5

#24.1 OR #24.2 OR #24.3 OR #24.4
#24.4
unconsciousness:de AND ('head injury'/exp OR tbi:ab,ti OR tbis:ab,ti OR 'brain injury':ab,ti OR 'brain injuries':ab,ti OR 'brain injured':ab,ti OR posttraumatic:ab,ti OR 'post-traumatic':ab,ti) AND [embase]/lim AND [1990-2012]/py
#24.3
'consciousness disorder':de OR 'consciousness disorder':ab,ti OR 'consciousness disorders':ab,ti OR 'disorders of consciousness':ab,ti AND [embase]/lim AND [1990-2012]/py
#24.2
'persistent vegetative state':de OR 'minimally conscious state':de OR 'vegetative state':ab,ti OR 'vegetative states':ab,ti OR 'minimal conscious state':ab,ti OR 'minimal conscious states':ab,ti OR 'minimally conscious state':ab,ti OR 'minimally conscious states':ab,ti OR 'unawareness state':ab,ti OR 'unawareness states':ab,ti OR 'posttraumatic confusional state':ab,ti OR ‘post-traumatic confusional state’:ab,ti OR ‘posttraumatic confusion state’:ab,ti OR ‘post-traumatic confusion state’:ab,ti OR 'posttraumatic confusional states':ab,ti OR ‘post-traumatic confusional stateS’:ab,ti OR ‘posttraumatic confusion states’:ab,ti OR ‘post-traumatic confusion states’ OR 'prolonged posttraumatic unawareness':ab,ti OR 'prolonged post traumatic unawareness':ab,ti OR 'prolonged unconscious state':ab,ti OR 'prolonged loss of consciousness':ab,ti AND [1990-2012]/py
#24.1
'coma'/exp AND [embase]/lim AND [1990-1992]/py

Embase
TREATMENT
#23.12
#23.8 AND #23.11
#23.11
#23.9 OR #23.10
#23.10
'rehabilitation'/exp OR rehabilitat*:ab,ti OR 'diet supplementation':de,ab,ti OR 'dietary supplement':ab,ti OR 'dietary supplements':ab,ti OR 'diet therapy'/exp OR 'diet therapy':ab,ti OR neutraceutical*:ab,ti OR pharmacologic*:de,ab,ti OR 'range of motion exercise':ab,ti OR 'range of motion exercises':ab,ti OR 'kinesiotherapy'/exp OR kinesiotherapy:ab,ti OR 'positioning protocol':ab,ti OR 'positioning protocols':ab,ti OR 'patient positioning':ab,ti OR 'body position':de OR 'body posture':de OR 'positional change':ab,ti OR 'positional changes':ab,ti OR 'postural change':ab,ti OR 'postural changes':ab,ti OR 'physiotherapy'/exp OR physiotherapy:ab,ti OR 'physical therapy':ab,ti AND [1990-2012]/py
#23.9
'bromocriptine'/exp OR 'amantadine'/exp OR 'dopamine receptor stimulating agent'/exp OR 'gabaergic receptor affecting agent'/exp OR 'sensory stimulation'/exp OR therap*:lnk,ab,ti OR 'therapy'/exp OR stimulation:ab,ti OR sensory:ab,ti OR 'tape recorder':de OR 'tape recording':ab,ti OR videorecording:de,ab,ti OR audiotape*:ab,ti OR deprivation:de,ab,ti OR 'hyperbaric oxygen':de,ab,ti OR treatment*:de,ab,ti OR lamotragine:ab,ti OR amitriptyline:de,ab,ti OR desipramine:de,ab,ti OR methylphenidate:de,ab,ti OR amantadine:ti,ab OR levodopa:de,ab,ti OR zolpidem:de,ab,ti OR baclofen:de,ab,ti OR 'dopaminergic drug':ab,ti

OR 'dopaminergic drugs':ab,ti OR 'gaba agent':ab,ti OR 'gaba agents':ab,ti OR 'gabaergic drug':ab,ti OR 'gabaergic drugs':ab,ti AND [1990-2012]/py
#23.8
#23.6 NOT #23.7
#23.7
'advanced directive':ti OR 'advanced directives':ti OR 'advance directive':ti OR 'advance directives':ti OR pope:ti OR papal:ti OR catholic*:ti OR theolog*:ti OR schiavo*:ti OR quinlan*:ti OR cruzan*:ti OR 'living will':ti OR 'living wills':ti OR jewish:ti OR wanglie*:ti OR torah:ti OR talmud:ti OR euthanasia:ti OR 'assisted suicide':ti OR 'right to die':ti OR 'right to life':ti OR 'assisted death':ti OR 'supreme court':ti OR christianity:ti OR muslim*:ti OR islam*:ti OR moral:ti OR morals:ti OR morality:ti OR 'john paul ii':ti OR 'death with dignity':ti OR legislation:ti OR bioethicist*:ti OR ethic*:ti OR legal*:ti AND [1990-2012]/py
#23.6
#23.5 AND ('article'/it OR 'article in press'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) AND ('case report'/de OR 'case study'/de OR 'clinical article'/de OR 'clinical protocol'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'human'/de OR 'human tissue'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'methodology'/de OR 'model'/de OR 'multicenter study'/de OR 'normal human'/de OR 'outcomes research'/de OR 'practice guideline'/de OR 'prospective study'/de OR 'questionnaire'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de)
#23.5
#23.1 OR #23.2 OR #23.3 OR #23.4
#23.4
unconsciousness:de AND ('head injury'/exp OR tbi:ab,ti OR tbis:ab,ti OR 'brain injury':ab,ti OR 'brain injuries':ab,ti OR 'brain injured':ab,ti OR posttraumatic:ab,ti OR 'post-traumatic':ab,ti) AND [embase]/lim AND [1990-2012]/py
#23.3
'consciousness disorder':de,ab,ti OR 'consciousness disorders':ab,ti OR 'disorders of consciousness':ab,ti AND [embase]/lim AND [1990-2012]/py
#23.2
'persistent vegetative state':de OR 'minimally conscious state':de OR 'vegetative state':ab,ti OR 'vegetative states':ab,ti OR 'minimal conscious state':ab,ti OR 'minimal conscious states':ab,ti OR 'minimally conscious state':ab,ti OR 'minimally conscious states':ab,ti OR 'unawareness state':ab,ti OR 'unawareness states':ab,ti OR 'posttraumatic confusional state':ab,ti OR ‘post-traumatic confusional state’:ab,ti OR ‘posttraumatic confusion state’:ab,ti OR ‘post-traumatic confusion state’:ab,ti OR 'posttraumatic confusional states':ab,ti OR ‘post-traumatic confusional stateS’:ab,ti OR ‘posttraumatic confusion states’:ab,ti OR ‘post-traumatic confusion states’ OR 'prolonged posttraumatic unawareness':ab,ti OR 'prolonged post traumatic unawareness':ab,ti OR 'prolonged unconscious state':ab,ti OR 'prolonged loss of consciousness':ab,ti AND [embase]/lim AND [1990-2012]/py
#23.1
'coma'/exp AND [embase]/lim AND [1990-1992]/py

Cochrane
DIAGNOSIS
ID Search
#1 MeSH descriptor Consciousness Disorders, this term only
#2 MeSH descriptor Persistent Vegetative State, this term only
#3 (vegetative state* OR consciousness disorder* OR unawareness state* OR disorders of consciousness OR prolonged loss of consciousness OR prolonged unconscius state* OR minimally conscious state* OR minimal conscious state OR posttraumatic confusion state* OR posttraumatic confusional state* OR prolonged posttraumatic unawareness):ti,ab,kw
#4 (#1 OR #2 OR #3)
#5 (#4), from 1990 to 2012
#6 MeSH descriptor Neuroimaging explode all trees
#7 (imaging*):ti,ab,kw
#8 MeSH descriptor Neurologic Examination explode all trees
#9 MeSH descriptor Diagnosis, Differential explode all trees
#10 MeSH descriptor Diagnosis, this term only
#11 (diagnos*):ti,ab,kw
#12 MeSH descriptor Diagnostic Errors explode all trees
#13 MeSH descriptor Diagnostic Techniques, Neurological explode all trees
#14 MeSH descriptor Tomography explode all trees
#15 (tomography OR brain mapping):ti,ab,kw
#16 (pet scan*):ti,ab,kw
#17 MeSH descriptor Magnetic Resonance Spectroscopy explode all trees
#18 (magnetic resonance spectroscopy OR evoked potential*):ti,ab,kw
#19 MeSH descriptor Evoked Potentials explode all trees
#20 MeSH descriptor Echoencephalography explode all trees
#21 MeSH descriptor Electroencephalography explode all trees
#22 (electroencephalogra* OR EEG OR eegs OR Qeeg or qeegs):ti,ab,kw
#23 MeSH descriptor Electromyography explode all trees
#24 (ELECTROMYOGRAPH* OR EMG OR EMGs):ti,ab,kw
#25 MeSH descriptor Neuroradiography, this term only
#26 (instrument OR instruments OR measure OR measures OR scale OR scales OR SCORE OR scores OR INDEX OR INDICES):ti,ab,kw
#27 (ELECTROPHYSIOLOGIC TECHNIQUE OR FMRI OR mri OR MRIS OR NUCLEAR MAGNETIC RESONANCE OR NMR SPECTROSCOPY OR MR SPECTROSCOPY OR COGNITIVE EP* OR EVENT RELATED POTENTIAL*):ti,ab,kw
#28 (SPECT OR SPECTS OR CT SCAN* OR CT X-RAY OR CINE-CT OR TOMODENSITOMETRY OR SENSORY MODALITY ASSESSMENT OR SENSORY STIMULATION ASSESSMENT):ti,ab,kw
#29 (WESSEX HEAD INJURY MATRIX OR WESTERN NEURO SENSORY STIMULATION PROFILE)
#30 MeSH descriptor Sensitivity and Specificity explode all trees
#31 MeSH descriptor Predictive Value of Tests explode all trees
#32 (PREDICTIVE):ti,ab,kw and (VALUE):ti,ab,kw
#33 MeSH descriptor Confidence Intervals explode all trees

#34 (DETECT* OR CHARACTERISTIC* OR COMMAND* OR CATEGORIZ* OR CATEGORIS* OR DISTINGUISH* OR DIFFERENTIAT* OR BEHAVIOURAL ASSESSMENT* OR BEHAVIORAL ASSESSMENT* OR BEHAVIOR ASSESSMENT* BEHAVIOUR ASSESSMENT*):ti,ab,kw
#35 MeSH descriptor Neuropsychological Tests, this term only
#36 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)
#37 (#36 AND #5)

Cochrane
PROGNOSIS
#1 MeSH descriptor Consciousness Disorders, this term only
#2 MeSH descriptor Persistent Vegetative State, this term only
#3 (vegetative state* OR consciousness disorder* OR unawareness state* OR disorders of consciousness OR prolonged loss of consciousness OR prolonged unconscius state* OR minimally conscious state* OR minimal conscious state OR posttraumatic confusion state* Or posttraumatic confusional state* OR prolonged posttraumatic unawareness):ti,ab,kw
#4 (#1 OR #2 OR #3)
#5 (#4), from 1990 to 2012
#43 MeSH descriptor Treatment Failure explode all trees
#44 MeSH descriptor Disease Progression explode all trees
#45 MeSH descriptor Convalescence explode all trees
#46 MeSH descriptor Treatment Outcome explode all trees
#47 (recover OR recovers OR recovery OR recovering OR recoveries OR functional level OR improve* OR improving OR emerge OR emerges OR emerged OR emergence OR emerging OR restoration OR restore* OR outcome* OR prognos* OR predict* OR clinical course* OR progress* OR recuperat* OR convalescence OR convalesce OR convalesced OR convalesces OR convalescing OR nomogram*):ti,ab,kw
#48 (#38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47)
#49 (#5 AND #48)

Cochrane
TREATMENT
#1 MeSH descriptor Consciousness Disorders, this term only
#2 MeSH descriptor Persistent Vegetative State, this term only
#3 (vegetative state* OR consciousness disorder* OR unawareness state* OR disorders of consciousness OR prolonged loss of consciousness OR prolonged unconscius state* OR minimally conscious state* OR minimal conscious state OR posttraumatic confusion state* OR posttraumatic confusional state* OR prolonged posttraumatic unawareness):ti,ab,kw
#4 (#1 OR #2 OR #3)
#5 (#4), from 1990 to 2012
#50 MeSH descriptor Hyperbaric Oxygenation explode all trees
#51 MeSH descriptor GABA Agents explode all trees
#52 MeSH descriptor Drug Therapy explode all trees

#53 MeSH descriptor Dietary Supplements explode all trees
#54 MeSH descriptor Physical Therapy Modalities explode all trees
#55 Any MeSH descriptor with qualifier: DT
#56 Any MeSH descriptor with qualifier: TH
#57 (sensory OR stimulation OR tape recording* OR audiotape* OR videotape* OR deprivation OR hyperbaric oxygen* OR treatment* OR therapies OR therapeutic):ti,ab,kw
#58 MeSH descriptor Bromocriptine explode all trees
#59 (lamotragine):ti,ab,kw
#60 MeSH descriptor Amitriptyline explode all trees
#61 MeSH descriptor Desipramine explode all trees
#62 MeSH descriptor Methylphenidate explode all trees
#63 MeSH descriptor Amantadine explode all trees
#64 MeSH descriptor Levodopa explode all trees
#65 (zolpidem):ti,ab,kw
#66 MeSH descriptor Baclofen explode all trees
#67 MeSH descriptor Dopamine Agents explode all trees
#68 (dopaminergic drug* OR gabaergic drug* OR rehabilitat* OR dietary supplement* OR neutraceutical* OR pharmaclogic* OR range of motion exercise* OR positioning protocol* OR positional change* OR postural change* OR physical therapy OR physiotherapy):ti,ab,kw
#69 (#50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68)
#70 (#5 AND #69)

Appendix e-6. AAN rules for classification of evidence for risk of bias

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.

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.

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.

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.

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.

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.

Therapeutic scheme

Class I

A randomized controlled clinical trial 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 2 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 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

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 above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). (Alternatively, a randomized crossover trial missing 1 of the following 2 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.

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 2 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.

*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any 1 of the 3 is missing, the class is automatically downgraded to Class III.

**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).

Appendix e-7. Rules for determining confidence in evidence

- Modal modifiers used to indicate the final confidence in evidence in the conclusions
    - High confidence: highly likely or highly probable
    - Moderate confidence: likely or probable
    - Low confidence: possibly
    - Very low confidence: insufficient evidence
- Initial rating of confidence in the evidence for each intervention outcome pair
    - High: requires 2 or more Class I studies
    - Moderate: requires 1 Class I study or 2 or more Class II studies
    - Low: requires 1 Class II study or 2 or more Class III studies
    - Very low: requires only 1 Class III study or 1 or more Class IV studies
- Factors that could result in downgrading confidence by 1 or more levels
    - Consistency
    - Precision
    - Directness
    - Publication bias
    - Biological plausibility
- Factors that could result in downgrading confidence by 1 or more levels or upgrading confidence by 1 level
    - Magnitude of effect
    - Dose response relationship
    - Direction of bias

Appendix e-8. Evidence synthesis tables

See evidence synthesis tables, by study type, available as separate data supplement files.

Diagnosis evidence table

Diagnostic Procedure	Reference Standard	Number & Class of Studies	Effect (e.g., sensitivity & specificity)	Precision	Consistent	Directness	Plausible	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
EMG for detecting responses to command			[Cannot combine because they use different methods of analysis]								

EMG for detecting responses to command	CRS-R used to assign a diagnosis of VS/UWS or MCS	1 Class I Habbal 2014[e31]	10 VS/UWS, 28 MCS (8 without response to command and 20 with response to command, MCS- and MCS+, respectively) Response to command for at least one command in 6 VS/UWS, 3 MCS-, 11 MCS+ (14 MCS): 6/10 VS and 14/28 MCS; sensitivity for MCS 0.5 (95% CI 0.31 to 0.69); specificity 0.0.4 (95% CI 0.14 to 0.73) ANOVA to make sure increased activity corresponded to area targeted by command: 1 VS/UWS, 3 MCS+; sensitivity for MCS 0.21 (95% CI 0.05 to 0.51), specificity 0.9 (95% CI 0.56 to 1.00) LR+ 2.14, 95% CI 0.26-17.72	DD	N/A	-	-	-	N/A	Anchored at moderate (1 Class I study), markedly decreased confidence in the evidence due to LR+ precision (not statistically significant but includes possibility of important LR+) There is insufficient evidence to support or refute the diagnostic value of the presence of EMG activity to command after adjusting for involuntary movements in distinguishing MCS from VS (LR+ 2.1, 95% CI 0.3-17.7) (very low confidence in the evidence, 1 Class I study with markedly decreased confidence in the evidence due to precision).	Very low

EMG for detecting responses to command	Diagnosis; definitions given in methods	1 Class I Lesenfants 2016[e37]	Using a threshold score of 1.5, 0/15 patients with VS/UWS, 2/8 patients with MCS-, and 14/14 patients with MCS+ demonstrated an EMG response to motor commands. A positive (above threshold) EMG response thus corresponds to a sensitivity of 73% (95% CI 50%–89%) and a specificity of 100% (95% CI 78%–100%) for distinguishing MCS (MCS- or MCS+) from VS/UWS. LR+ (using a continuity correction) of 23.0 (95% CI 1.5–355.6)	D	N/A	O	O	O	N/A	Anchored at moderate, decreased to low given precision. 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 with decreased confidence in the evidence due to precision).	Low
EEG background rhythm		2 Class I Estraneo 2016[e35]	A random effects meta-analysis of the sensitivity and specificity values from these two studies resulted in a sensitivity of 46% (95% CI 19%-74%, I2 78%) and a specificity of 92% (95% CI 69%–100%, I^2 = 61%) when assessing the value of normal or	D	D	o	o	o	N/A	Anchored at moderate because only one of the Class II studies could drive a conclusion on its own based on specificity[35]; double downgraded because meta-analysis not statistically significant but includes possibility of important LR+ and downgrade for consistency	Very low

			mildly abnormal EEG background rhythm for a diagnosis of MCS (vs VS/UWS).							because two studies are not consistent)	
Long-term EEG background	CRS-R in 38 of 44 subjects, std exam in 6 pts	Class I (for EEG data) Forgacs 2014[e33]	44 subjects (62 adm); traumatic in 28, anoxic/hypoxic in 6, and 2 stroke, 2 hemorrhagic stroke, 2 SAH, and 2 mixed 6 mo to 26 years post-injury SOME PATIENTS EMCS; 31 PATIENTS VS OR MCS Pts in MCS often had normal or only mildly abnormal EEG bckgrd rhythms (15/23; 65%, 95% CI 45-81%); VS 2/8 (25%, 95% CI 7-59%) (from text, not including EMCS) All pts with MCS and evidence of command-following on fMRI had normal/mildly abnl awake EEG (3/3) OR for normal or mildly abnl EEG suggesting MCS 5.6, 95% 1.0-29.4) One pt with MCS had								

			several abnl awake EEG bckgrd (1/14, 7%, 95% CI 1-31%) so this finding cannot reliably exclude MCS Sensitivity of nl/mild abnl EEG for MCS (vs VS) 65% (45-81%); specificity 75% (36-96%) One patient with MCS had a severely abnormal awake EEG background (1/23, 4%, 95% CI 0.7% to 21%) "In the entire cohort, EEG organization and overall brain metab showed no signif assoc with bedside behav testing"								
Routine EEG background	DoC category based on diagnostic criteria; CRS-R also performed	Class I Estraneo 2016[e35]	2/36 patients with MCS had normal or mildly abnormal EEG backgrounds (33%, 95% CI 20%–50%, 1/11 MCS- and 11/25 MCS+) vs 0/37 patients with VS/UWS (0%, 95% CI 0%–9%). The sensitivity of a normal or mildly abnormal EEG background rhythm for a diagnosis of MCS (vs VS/UWS) was 33% (95% CI								

			19%–51%) and the specificity was 100% (95% CI 88%–100%). Poor EEG organization (categorized as moderately abnormal, diffuse slowing, or low voltage) was present in the remainder of patients, with one MCS+ patient identified has having low voltage.								
EEG reactivity											
EEG reactivity	DoC category based on diagnostic criteria; CRS-R also performed	Class I Estraneo 2016[e35]	Eighteen of 37 patients with VS/UWS and 35/36 patients with MCS had reactivity to at least one kind of stimuli (sensitivity for MCS 97%, 95% CI 85%–100%, specificity 51%, 95% CI 24%–68%, LR+ 2.00, 95% CI 1.43-2.80). Results were similar when using reactivity to at least one kind of stimuli to distinguish VS/UWS from MCS-, where sensitivity was high (91%, 95% CI 59%–100%) for diagnosing MCS- in the presence of EEG reactivity but	D	NA	o	o	o	N/A	Downgrade by one for imprecision due to unimportant LCI (< 2); small importance at most It is possible that EEG reactivity to at least one kind of stimuli distinguishes MCS from VS to a mildly important degree (low confidence in the evidence; one Class I study with decreased confidence in the evidence due precision; LR+ 2.00, 95% CI 1.43-2.80).	Low

			specificity was low (51%, 95% CI 34%–68%). Other EEG reactivity results are also described in the study but not presented here. Of note, patients with anoxic DoC were generally less responsive to stimuli than patients with traumatic or vascular insults.								
EEG reactivity + Background rhythm											
EEG reactivity + Background rhythm	DoC category based on diagnostic criteria; CRS-R also performed	Class I Estraneo 2016[e35]	Combining a low voltage background EEG pattern and the lack of EEG reactivity better distinguished VS/UWS from MCS-. This combination was present in 20/37 patients with VS/UWS and 1/10 patients with MCS-, resulting in high sensitivity for a diagnosis of VS (91%, 95% CI 59%–100%) and a specificity of 54% (95% CI 37%–71%) LR+ of 5.4 (95% CI 0.82–35.5)	DD	NA	o	o	o	NA	There is insufficient evidence to support or refute the diagnostic value of combining a low voltage background EEG pattern and the lack of EEG reactivity for distinguishing VS/UWS from MCS (very low confidence in the evidence, 1 Class I study with markedly decreased confidence in the evidence due to precision; LR+ 5.4, 95% CI 0.82-35.5).	Very low
Specific entropy											

Specific entropy	Standardized behavioral evaluations that incorporate the Aspen criteria	1 Class III Gosseries 2011[e42]	ONLY CHRONIC PATIENTS MEET INCLUSION CRITERIA. In the chronic patients, sensitivity and specificity of the ROC analysis was described as too low to allow reliable conclusions to be drawn (area under the curve 0.5; 95% confidence interval 0.3-0.8). No numbers to calculate sensitivity, specificity, or LR+.	D	N/A	o	o	o	N/A	In the chronic group, sensitivity and specificity were described as too low to allow reliable conclusions to be drawn (area under the curve 0.5; 95% confidence interval 0.3-0.8) and CIs were wide	Very low
Evoked potentials											
P3a (exogenous) and P3b (endogenous) targets on EEG in response to binaurally presented word stimuli	CRS-R used to assign a diagnosis of VS or MCS	1 Class II Chennu 2013[e39]	Enrolled convenience sample of MCS, VS, and normal controls Exogenous attention (EEG): 1/9 VS patients and 3/12 MCS patients had attention; sensitivity for MCS 0.25 (95% CI 0.07 to 0.57) and specificity 0.89 (95% CI 0.51 to 0.99); LR+ 2.3, 95% CI 0.3–18.2 Endogenous attention (EEG): 1/9 VS patients and 0/12 MCS patients had attention; sensitivity for	DD	N/A	-	-	-	N/A	There is insufficient evidence to support or refute the diagnostic value of evidence of exogenous or endogenous attention as assessed by the P3a and P3b components of the P300 response occurring in response to word stimuli for distinguishing MCS from VS/UWS (very low confidence in the evidence, one Class II study with markedly decreased confidence in	Very low

			MCS 0 (95% CI 0 to 0.30) and specificity 0.89 (0.51 to 0.99); LR+ 0.26 with continuity correction, 95% CI 0.01–5.65 One patient thought to be in VS had exogenous and endogenous responses							the evidence due to precision; LR+ for exogenous attention 2.3, 95% CI 0.3-18.2, LR+ for endogenous attention 0.26, 95% CI 0.01-5.65).	
Laser evoked potentials (LEPs) to activate nociceptive pathways	CRS-R used to assign diagnosis of VS or MCS	1 Class I Naro 2015[e38]	38 DoC patients (15 MCS, 23 VS) All patients showed the N1P1 component of both Aδ-LEP and C-LEP. The Aδ-LEP N2P2 and C-LEP N2P2 components were present in 15/15 patients with MCS and 10/23 patients with VS/UWS (sensitivity for MCS 100%, 95% CI 78%–100%, specificity 57%, 95% CI 34%–77%). LR+ 2.30, 95% CI 1.44-3.67	D	NA	o	o	o	NA	Downgrade by one for imprecision due to unimportant LCI (<2); small importance at most 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 with decreased confidence in the evidence due precision; LR+ 2.30, 95% CI 1.43-3.67).	Very low
Laser evoked potentials (LEPs) to activate nociceptive pathways	CRS-R used to assign diagnosis of VS or MCS	1 Class I Naro 2015[e38]	38 DoC patients (15 MCS, 23 VS) Seven patients with VS/UWS showed neither Aδ-LEP N2P2 nor the C-LEP N2P2	DD	NA	o	o	o	NA	There is insufficient evidence to support or refute the diagnostic value of the absence of Aδ-LEP N2P2 nor the C-LEP N2P2	Very low

			(sensitivity for 30%, 95% CI 14%–53%; specificity 100%, 95% CI 75%–100%; LR+ with continuity correction 10.0, 95% CI 0.61–163.1)							components in response to LEPs for distinguishing VS/UWS from MCS (very low confidence in the evidence, 1 Class I study with markedly decreased confidence in the evidence due to precision; LR+ 10.0, 95% CI 0.61-163.1).	
PCI											
Perturbational Complexity Index (PCI) - based on quantification of EEG responses to TMS	CRS-R used to assign a diagnosis of VS/UWS, MCS+, or MCS-	1 Class I Casarotto 2016[e34]	CAN ONLY USE CHRONIC POPULATION; DID THIS USING SUPPL TABLE 28 VS, 28 MCS => PCI*> 0.31 in 27 MCS patients and 8 VS/UWS patients, < 0.31 in 1 MCS patient and 20 VS/UWS patients; PCI* > 0.31 has a 0.96 sensitivity (0.8-1.0) and 0.71 (0.51-0.86) specificity for MCS; LR+ 3.375 (1.87-6.09)	D	N/A	o	o	o	N/A	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 with decreased confidence in the evidence due to precision). (Since LCI is unimportant and UCI is important)	Low
Nasal cannula "sniff controller"											

Nasal cannula "sniff controller "	UWS/VS or MCS based on CRS-R assessments	1 Class I Charland-Verville 2014[e32]	Enrolled 14 MCS and 11 VS patients; 1 MCS patient had a response Sensitivity of positive breathing test for MCS: 7% (95% CI 0.2 to 22%) Specificity of positive breathing test for MCS: 100% (95% CI 68% to 100%) LR using continuity correction 2.4 (0.11-53.8)	DD	N/A	-	-	-	N/A	Anchored at moderate (1 Class I study), but markedly decreased confidence in the evidence due to precision for LR+ not statistically significant and includes important and unimportant LR+ There is insufficient evidence to support or refute the use of a nasal cannula "sniff controller" to distinguish MCS from VS (LR+ 2.4, 95% CI 0.11 to 53.8) (very low confidence in the evidence, 1 Class I study with markedly decreased confidence in the evidence due to precision).	Very low
fMRI											
fMRI using word counting task	CRS-R	1 Class I Monti 2015[e36]	A difference in activation between the two tasks was observed in 6/16 patients with MCS (6 MCS+, 0 MCS-) and 3/8 patients with VS (sensitivity for MCS 38%, 95% CI 15%–65%, specificity 63%, 96% CI 24%–91%). LR+ 1.00							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 with the LR+ suggesting no change in the probability of MCS with testing and CIs suggesting values of slight	Low

			(95% CI 0.33-2.99) However, the study notes that 7 patients had excessive movements precluding meaningful analysis (3 VS, 1 MCS-, 3 MCS+) due to excessive movement. If considering only those subjects with interpretable findings, 3/5 patients with VS and 6/12 patients with MCS showed differential activation (sensitivity for MCS 50%, 95% CI 21%–79%, specificity 40%, 95% CI 5%–85%; LR+ 0.83, 95% CI 0.33–2.08). The poor sensitivity and specificity partly reflect the fact that fMRI detected high-level cognitive processing in 3/8 patients (37.5%, 95% CI 13.7%–69.4%) without evidence of command following on the CRS-R, i.e., who were in VS/UWS.							importance at most; LR+ 1.00, 95% CI 0.33-2.99). Results were impacted by the fact that 3 of 8 patients diagnosed with VS/UWS due to 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.	

fMRI	CRS-R in 38 of 44 subjects, std exam in 6 pts	1 Class II (for fMRI data) Forgacs 2014[e33]	44 subjects (62 adm); traumatic in 28, anoxic/hypoxic in 6, and 2 stroke, 2 hemorrhagic stroke, 2 SAH, and 2 mixed 6 mo to 26 years post-injury SOME PATIENTS EMCS; 31 PATIENTS VS OR MCS 3/14 patients with MCS had evidence of covert command-following on fMRI; 0/6 in VS had evidence of covert command-following on fMRI Sensitivity for MCS 21% (6-51%); specificity 100% (52-100%); PPV 100% (31-100%) LR+ 3.3* (0.2-55.0)	DD	N/A	-	-	-	N/A	There is insufficient evidence to support or refute the use of command following on an fMRI motor imagery task to distinguish MCS from VS (LR+ 2.4, 95% CI 0.11 to 53.8) (very low confidence in the evidence, 1 Class II study with markedly decreased confidence in the evidence due to precision).	Very low

fMRI using incorrect-minus-correct activation protocol	CRS-R used to assign a diagnosis of VS/UWS or MCS	1 Class II Kotchoubey 2014[e40]	29 VS/UWS, 26 MCS 11 of 29 patients with VS showed significant brain responses to factually incorrect vs correct sentences (38%, 23%-56%) 5 of 26 MCS patients responded (19%, 95% CI 9%-38%) Positive response has 31% sensitivity for MCS (12%-59%) and 62% specificity for MCS (42%-79%) LR+ 0.51 (0.20-1.27)	D	N/A	_	_	_	N/A	Anchored at low, downgraded for precision (not statistically significant but includes possibility of mildly important value) There is insufficient evidence to support or refute the use of an fMRI incorrect-minus-correct activation protocol to distinguish MCS from VS (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision; LR+ 0.51, 95% CI 0.20-1.27). Results were impacted by the fact that 11 of 29 patients diagnosed with VS/UWS due to absence of command-following on the CRS-R had the suggestion of activation of language-related areas with the task (37.5%, 38%, 23%–56%), the implications of which are uncertain.	Very low

Resting state fMRI	Aspen Criteria	1 Class II Rosazza 2016[e41]	Full cohort: Resting state fMRI could not distinguish (OR 1.45, 95% CI 0.91-2.32; AUC 0.56, 95% CI 0.45-0.66). In the 85 patients who had FDG-PET, resting state fMRI could not distinguish (OR 1.54, 95% CI 0.89-2.68; AUC 0.57, 95% CI 0.45-0.69). Data were insufficient for calculation of sensitivity and specificity.	D	NA	o	o	o	NA	Anchored at low (conclusion AGAINST use), but downgrade for precision because CIs include possibility of a small important value; thus very low There is insufficient evidence to support or refute whether resting state fMRI is helpful in distinguishing between VS and MCS (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision, OR 1.45, 95% CI 0.91-2.32).	Very low
Other imaging											
Structural MRI, FDG-PET	Aspen Criteria	1 Class II Rosazza 2016[e41]	1 Class II study examined the use of structural MRI, resting state fMRI, and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) to assess default-mode network integrity for distinguishing between 72 patients in VS/UWS, 36 patients in MCS, and 11							Anchored at low (conclusion FOR use), but downgrade for precision (for both structural MRI and FDG-PET because LCIs go into the unimportant range) => very low There is insufficient evidence to support or refute whether structural MRI (OR 2.84, 95% CI 1.58-5.11)	Very low

			patients with severe disability. Injury to the default-mode network on imaging was assessed by blinded raters. Supplemental materials describe that structural MRI could distinguish between VS and MCS (OR 2.84, 95% CI 1.58-5.11; AUC 0.72, 95% CI 0.62-0.81) whereas resting state fMRI could not (OR 1.45, 95% CI 0.91-2.32; AUC 0.56, 95% CI 0.45-0.66). In the 85 patients who had FDG-PET, fMRI could again distinguish between VS and MCS (OR 3.14, 95% CI 1.56-6.34; AUC 0.73, 95% CI 0.62-0.84) as could FDG-PET (OR 2.06, 95% CI 1.37-3.11; AUC 0.75, 95% CI 0.64-0.87) but not resting state fMRI (OR 1.54, 95% CI 0.89-2.68; AUC 0.57, 95% CI 0.45-0.69). Data were insufficient for calculation of sensitivity							or FDG-PET (OR 2.06, 95% CI 1.37-3.11) are helpful in distinguishing between VS and MCS (very low confidence in the evidence, 1 Class II study with decreased confidence in the evidence due to precision).	

			and specificity.								
Diffusion tensor imaging (DTI)	Categorization based on CRS-R	1 Class III Zheng 2017[e45]	CANNOT CALCULATE MEAURES OF DIAGNOSTIC ACCURACY, SO CLASS IV There is some discuss of accuracy, but there is no consistent reporting of data that would allow calculations as for other studies above								
NPLOs and mismatch negativity											
NPLOs and mismatch negativity	Standardized behavioral evaluations that incorporate the Aspen criteria	1 Class III Holler 2011[e43]	REMOVED FROM ANALYSIS BECAUSE INCLUDES A PATIENT WITH < 28 DAYS DOC. In 11/15 healthy controls, 0/6 MCS patients and 2/16 VS patients, MMN was detected. When comparing patient groups to healthy controls, Fisher's exact test revealed an overall difference between subgroups; (F(2, 35) =	D (Fisher s exact)	N/A	D	-	-	N/A	Directness- Neither ERPs nor NPLOs could reliably distinguish MCS from VS patients (only conscious from unconscious). There is insufficient evidence to support or refute EEG assessment paradigms that utilize mismatch negativity in differentiating MCS and VS/UWS (very low confidence in the evidence, 1 Class III study with limited	Very low

			12.12; p < 0:001). There was a significant difference between healthy subjects and MCS patients (F(1, 20) = 10.57; p < 0:01) and between healthy subjects and VS patients (F(1, 30) = 13.29; p < 0:01) but not between MCS and VS patients (F(1; 21) < 0:001; p > 0:99). 73% of healthy controls but only 12.5% of VS patients and no MCS patients showed significant MMN. The contrast between VS patients and healthy subjects yielded a sensitivity of 0.88, a specificity of 0.73, and an efficiency of 0.81. When MCS patients were grouped with healthy controls (ie, conscious group), specificity dropped to 0.52 and efficiency to 0.68. In the NPLO analysis, the overall sensitivity for							precision). There is insufficient evidence to support or refute non–phase-locked oscillations for diagnosing disorders of consciousness (1 Class III study with limited precision).	

			MMN in NPLOs when comparing healthy controls and VS patients was 0.69, while the specificity was 0.93, resulting in the same efficiency as for ERPs, i.e., 0.81. When MCS patients were grouped with healthy controls, specificity and efficiency remained high at 0.90 0.81, respectively. Conclusions: Neither ERPs nor NPLOs could reliably distinguish MCS from VS patients. However, NPLOs were more sensitive than ERPs for detecting differential activity between the conscious (NC + MCS) and unconscious (VS) subgroups, suggesting more precise identification of active cognitive processing. Significance: Intact neurophysiological attentional responses observed in the NPLOs of VS patients may indicate a								

			need for other diagnostic techniques. Inter-individual differences in the direction of the effect should be considered as normal variance.								
DRS	CRS-R	1 Class IV Doiron 2014[e114] (would be Class II but no measures of statistical precision calculable)	[Abstract only, 183 patients aged 16-64 at 4-16 weeks post-injury with TRAUMATIC MCS versus VS) 32% of subjects in MCS were incorrectly identified as VS or extreme VS using DRS total score >21 "There was no DRS total score cut-off that was both highly sensitive and specific to MCS" Total score <21 highly predictive of MCS (PPV=0.95) and a total score of >24 was highly predictive of VS (NPV=0.88) Abstract conclusion = DRS should not be used for DDx but	D	NA	-	-	-	NA	Very low (1 Class IV, no measure of statistical precision)	

			DRS may help with screening								
FDG PET	Standardized behavioral eval that incorporate the Aspen criteria	1 Class II Stender 2014[e44]	We recorded agreement between CRS–R and PET imaging results in 95 of 112 (85%) cases. Demographic and clinical data did not differ significantly between the patients who were examined and those who were not. All scans were of good quality. The sensitivity to identify behavioral minimally conscious state as defined by CRS–R was 93% (85–98; table 3). Time since injury did not correlate with diagnosis according to 18F-FDG PET (phi=–0.123, p=0.99). Traumatic cause correlated with a diagnosis of minimally conscious states (phi=0.324, p=0.01).	N/A	N/A	-	-	-	N/A	EXCLUDED BECAUSE CANNOT SEPARATE PATIENTS < VS >28 DAYS POST-INJURY Other: 25/122 cases were < 28 days post-injury. Unable to specifically determine how many of these cases were represented in the sensitivity/specificity analysis (CRS-R v. PET). Not clear if investigators responsible for reference standard (CRS-R) were blind to clinical consensus dx.	Low

fMRI	Standardized behavioral eval that incorporate the Aspen criteria	1 Class II Stender 2014[e44]	The active fMRI method had lower sensitivity for diagnosis of MCS (45%, 30–61%), and lower overall congruence with behavioral scores (63%, 51–73%) than PET imaging. 13 of 42 (32%) of the behaviorally unresponsive patients (ie, diagnosed as unresponsive with CRS–R) showed brain activity compatible with (minimal) consciousness (ie, activity associated with consciousness, but diminished compared with fully conscious individuals) on at least one neuroimaging test.	N/A	N/A	D	-	-	N/A	EXCLUDED BECAUSE CANNOT SEPARATE PATEINTS < VS >28 DAYS POST-INJURY Directness: 41% (71/122) of MCS patients could not be scanned using fMRI imagery due to movement requiring sedation. Other: 25/122 cases were < 28 days post-injury. Unable to specifically determine how many of these cases were represented in the sensitivity/specificity analysis (CRS-R v. fMRI); Not clear if investigators responsible for reference standard (CRS-R) were blind to clinical consensus dx.	Low
Consensus-based diagnosis	Standardized behavioral rating scales that incorporate the Aspen criteria (CRS-R)	1 Class II Stender 2014[e44]	All 126 patients who received a clinical consensus diagnosis before admission were included irrespective of the clinical difficulty of obtaining a diagnosis (table 2). However, in 33 cases (27%), this diagnosis was	N/A	N/A	D ?	-	-	U?	EXCLUDED BECAUSE CANNOT SEPARATE PATEINTS < VS >28 DAYS POST-INJURY Magnitude of effect: The low sensitivity of clinical consensus diagnosis to MCS is a very important finding. The concern about the number of	Low

			ambiguous or not in accordance with commonly acknowledged clinical entities (eg, post-comatose state). When we excluded patients with an ambiguous clinical consensus diagnosis, CRS–R and the clinical consensus diagnosis scores agreed in 69 of 89 people (78%, 95% CI 68–85) of cases (table 3). The sensitivity of clinical consensus diagnosis of minimally conscious state was 67% when compared against the diagnosis according to CRS–R (table 3).							cases that were <28 days and how they were distributed in the probability matrix applies to this analysis as well. Note that 27% (33) of cases were excluded from this analysis b/c the consensus dx was ambiguous.	

Therapeutic evidence synthesis table

Intervention	Outcome	Number & Class of Studies	Effect	Precision	Consistent	Directness	Plausible	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
Amantadine		1 Class 1, 1 Class IV	(See below)	-	N/A	-	-	-	N/A	Amantadine probably improves rate of improvement in traumatic brain injury patients with VS or MCS (moderate confidence in evidence, 1 Class I study).	Moderate (1 Class I)
Amantadine	Rate of improvement on DRS, DRS, CRS-R	One Class I Giacino 2012[e80] and 1 Class IV study Whyte 2013[e89]; *anchor = moderate confidence in evidence (one Class I and one Class IV)*	Amantadine gp recovered faster (difference in slope of DRS score, 0.24 points per week; *p* = 0.007) at 4 weeks. Rate of improvement in the amantadine group slowed during the 2 weeks after treatment (weeks 5 and 6) and was significantly slower than the rate in the placebo group (difference in slope, 0.30 points per week; *p* = 0.02). Overall improvement in DRS scores between baseline and week 6 (2 weeks after	-	N/A	-	-	-	N/A	Amantadine probably improves rate of improvement in traumatic brain injury patients with VS or MCS (moderate confidence in evidence, 1 Class I study).	Moderate (1 Class I)

			treatment was discontinued) was similar in the two groups. Amantadine also led to faster recovery in Class IV study. Katz 2016[e115] abstract re prognostic analysis of amantadine data originally Class I but also ends up being Class IV because no calculable measures of association for the key results for this question.)								
Zolpidem		Two Class IV Du 2014[e116], Whyte 2014[e116]		D	-	D	-	-	N/A	There is insufficient evidence to support or refute the use of zolpidem in patients with prolonged disorders of consciousness (very low confidence in the evidence, 2 Class IV studies).	Very low (2 Class IV studies)
Zolpidem	SPECT and digital cerebral state monitor (CSM) which included CSI, burst suppression (BS), and EMG	One Class IV Du 2014[e116] (case series)	1 hour after treatment with zolpidem, CSI of brain contrecoup contusion and compression injury groups were better than pre-tx ($p<0.05$); BS also lower after tx; no change in EMG in any	-	N/A	D	-	-	N/A	Already Class IV and anchored at very low confidence but would downgrade further because of indirect outcome measures (unclear how these	Very low (1 Class IV study)

			of four groups; only p-values provided in text; some #s in tables but clinical significance unclear							relate to clinically relevant changes)	
Zolpidem	% probable responders	One Class III Whyte 2014[e117] based on study design/no comparison of baseline characteristics but Class IV since unable to calculate measures of effect	No usable results are presented: there is no paired comparison of change on placebo vs change on zolpidem in phase 1 or phase 2. Without this comparison, the response rate of 28 probable responders in phase 1 and 4 definite responders in phase 2 are meaningless. There was inevitably some noise in the study related to patients improving after placebo. We need to know the number of patients that improved on placebo and drug, improved on drug and not placebo, improved on placebo and not drug and improved on neither. Without this information there is no way to determine the	D	-	-	-	-	N/A	Class IV because no calculable measures of effect or Class III/downgrade for precision because no statistical precision reported; either way, this ends up being Class IV	Very low (1 Class IV study)

			contribution from random error. The confidence interval the authors calculated comes from a single sample proportion 4/83. This is simply incorrect. The correct analysis might show no significant difference—we cannot tell.								
Single vs multiple neurostimulants		1 Class IV (due to no masking/blinding) Herrold 2014[e82]	DOCS change 4.12 +/- 12.69 in one stimulator group, 1.79 +/- 14.2 in multiple stimulator group; mean difference -2.33, 95% CI -7.7 to 3.072. If considering recovery of full consciousness at one year of injury, that occurred in 64% of multiple stim (54/84) and 57% of single (18/31), which corresponds to an OR of 1.3, 95% CI 0.6 to 3.0	D	N/A	-	-	-	-		Very low (1 Class IV study)
Single versus multiple neurostimulants (amantadine, bromocriptine, levodopa, methylphenidate, modafinil) during rehab	Recovery of consciousness during rehab, recovery within one year, change in DOCS-25 score above	1 Class IV (due to no masking/blinding) Herrold 2014[e82]	DOCS change 4.12 +/- 12.69 in one stimulator group, 1.79 +/- 14.2 in multiple stimulator group; mean difference -2.33, 95% CI -7.7 to 3.072. If considering	D	N/A	-	-	-	-		Very low (1 Class IV study)

	MDC, MCID		recovery of full consciousness at one year of injury, that occurred in 64% of multiple stim (54/84) and 57% of single (18/31), which corresponds to an OR of 1.3, 95% CI 0.6 to 3.0								
Various medications		One Class IV Whyte 2013[e89]; *anchor = very low confidence in evidence (one Class IV)*	Amantadine led to faster DRC improvement of all meds recorded. Dantrolene led to slowest DRC improvement. Neither med improved time to follow commands.	D	N/A	-	-	-	N/A	Downgrade for precision because the study has insufficient precision to exclude an association because of small sample sizes for medications; dantrolene exposure was associated with worse outcome but there were confounders	Very low (1 Class IV study)
Different medications: amantadine (see above), B-blockers, anticonvulsants, serotonergics, trazodone, methylphenidate, phenytoin, carbamazepine, dantrolene, benzos, baclofen, clonidine neuroleptics (see Table 3)	(1) DRS at 16 weeks; (2) time to regain ability to follow commands	1 Class IV Whyte 2013[e89]; *anchor = very low confidence in evidence (1 Class IV)*	Amantadine led to faster DRC improvement of all meds recorded. Dantrolene led to slowest DRC improvement. Neither med improved time to follow commands.	D	N/A	-	-	-	N/A	Downgrade for precision because the study has insufficient precision to exclude an association because of small sample sizes for medications; dantrolene exposure was associated with worse outcome but there were confounders	Very low (1 Class IV study)

Sensory Stimulation											
IMS program of sensory stimulation	Glascow Outcome Scores	1 Class IV Doman 2007[e118]; *anchor = very low confidence in evidence (one Class IV)*	34.5% of the IMS group made a moderate-good recovery on GOS, 9% remained in PVS, 56.5% out of coma but severely disabled.	-	N/A	D	-	-	N/A	Limited generalizability (directness) because enrolled people at one center with a therapy that is very center-dependent and because poor control gp (those patients whose family refused participation)	Very low (1 Class IV study)
Tilt table + integrated stepping device	Change in CRS-R at 3, 6 weeks	1 Class I Krewer 2015[e81]	Both groups improved at follow-up compared with baseline. When comparing median change scores from baseline to follow up, conventional treatment was superior to the tilt table with the integrated robotic stepping device at 3 weeks (immediately post treatment) (median [25%-75% percentile] for the stepping device group 3 [0–5] vs. conventional tilt table 4 [3–8]; U-test; U = 144.5, z = -2.299 p = .021, r = -.34) and 6 weeks	o	N/A	o	o	o	N/A	No placebo control group.	Moderate (1 Class I)

			(stepping device group 4 [-1 to 6] vs. conventional tilt table 9 [5–10]; U-test; U = 122.0, z = -2.824, p = .005, r = -.42).								
Fetal stem cell transplantation		1 Class IV Seledtsov 2005[e119]; *anchor = very low confidence in evidence (one Class IV)*	See Table e-3. Exper gp had less lethal and unsatisfactory outcomes, similar satisfactory outcomes, and more good outcomes compared with controls.	-	N/A	-	-	-	N/A		Very low (1 Class IV study)
Fetal stem cell transplantation	Glascow Outcome Classification; death, unsatisfactory, satisfactory, good	1 Class IV Seledtsov 2005[e119]; *anchor = very low confidence in evidence (one Class IV)*	See Table e-3. Exper gp had less lethal and unsatisfactory outcomes, similar satisfactory outcomes, and more good outcomes compared with controls.	-	N/A	-	-	-	N/A		Very low (1 Class IV study)
Autologous stem cells	Good outcome on Glasgow scale (4-5 points)	1 Class IV Kondratiev 2012[e120]; conference abstract only)	Within 12 months after injury, 4/15 pts in tx gp and 5/15 pts in control gp (OR 0.73, 95% CI 0.16 to 3.27) had good disease outcome. They say in text, "However, patients of the	D	N/A	-	-	-	N/A	Downgraded for precision given wide CIs with possible clinically important O.R.s in both directions	Very low (anchored at very low as no evidence of masking; would also have decreased confiden

			experimental gp, regained consciousness, indicated a more rapid and better recovery of cognitive and motor function, compared with similar patients of the control group," but no supporting info provided.								ce due to precision)
Autologous stem cells	Good outcome on Glasgow scale (4-5 points)	1 Class IV study (Class IV because no evidence of masked or blinded outcome assessment, though there is a control group) Kondratiev 2012[e120]; conference abstract only)	Within 12 months after injury, 4/15 pts in tx gp and 5/15 pts in control gp (OR 0.73, 95% CI 0.16 to 3.27) had good disease outcome. They say in text, "However, patients of the experimental gp, regained consciousness, indicated a more rapid and better recovery of cognitive and motor function, compared with similar patients of the control group," but no supporting info provided.	D	N/A	-	-	-	N/A	Downgraded for precision given wide CIs with possible clinically important O.R.s in both directions	Very low (anchored at very low as no evidence of masking; would also have decreased confidence due to precision)
Deep brain stimulation (DBS)											

	Poorly defined - "neurological changes" and whether they showed "clearly discernable behavioral evidence of consciousness every month for 1 year"	1 Class IV study Yamamoto 2010[e83]; *anchor = very low confidence in evidence (1 Class IV)*	Eight of the patients recovered from VS and were able to obey verbal commands at 13 and 10 months in the case of head trauma and at 19, 14, 13, 12, 12 and 8 months in the case of vascular disease after comatose brain injury, and no patients without DBS recovered from VS spontaneously within 24 months after brain injury.	-	N/A	-	-	-	N/A		Very low (1 Class IV study)
	Following instructions; "we devised a neurologic follow-up outcome scale for VS…" (Table 5)	1 Class IV study Yamamoto 2013[e84] for therapeutic, Class III for prognostic	21 patients with VS and 5 MCS patients treated with DBS. This almost certainly overlaps with study above as again, 8 of 21 patients recovered from VS and were able to follow verbal instructions. Compared patients who met electrophysiologic criteria (10/21 VS patients and 5/5 MCS patients) versus those who did not (11 VS, 0 MCS). Additionally, 6 patients in the non-DBS	-	N/A	-	-	U?	N/A		Very low (1 Class IV study)

			group met electrophysiologic criteria but family declined DBS. So for patients who received DBS, a positive electrophys profile was associated with an increased odds of recovery after DBS (8/10 vs 0/11 or 0.15/11.5, OR 88.0, 95% CI 5.4 to 1219.0; this goes more with response to treatment). For patients meeting electrophys criteria, 8/10 who received DBS recovered and 0/6 who did not recovered (or 0.5/6.5), for an OR of 48.0, 95% CI 2.9 to 679.9)									
Articles that were initially included but then excluded:											
BCAA supplementation* (*Mean of 47 days post-injury at enrollment (19 - 90 days), excluded for not meeting inclus crit) **Note: HBO article not included because it did not meet*	Change in DRS score as measured by log10DRS score	1 Class II Aquilani 2008[e121]; *anchor = weak confidence in evidence (one Class II)*	Log10DRS score improved significantly only in patients who had received BCAAs (log10DRS score, 1.3650.08 to 1.2940.05; P.001). Log10DRS score in the placebo		N/A						

inclusion criteria for guideline			recipients remained virtually unchanged (log10DRS score, 1.3730.03 to 1.370.03; P not significant). The difference in improvement of log10DRS score between the 2 groups was highly significant (P.000). Moreover, 68.2% (n15) of treated patients achieved a log10DRS point score of .477 or higher (3 as geometric mean) that allowed them to exit the vegetative or minimally conscious state.								
Spinal cord stimulation* *Not included in table above because in this paper (used for DBS), n=10 for SCS and no control group*		Yamamoto 2013[e84]									
Hyperbaric oxygen (HBOT)* *This was selected for inclusion but not placed in table because while there are 20 total patients, only 15 have a DoC>1*		Sahni 2012[e122]									

month and thus this does not meet inclusion criteria											
Sensory Stimulation* *This was selected for inclusion but it does not say how long that patients have been in a DoC other than that 21 of 29 patients were over a year post-injury, but no info about DoC duration in others and thus this does not meet criteria*	CRS-R	Schnakers 2014[e123]; abstract only	ABAB time-series design								

Prognosis for response to therapy evidence table

Intervention	Prognostic Factor	Outcome	Number & Class of Studies	Effect	Precision	Consistent	Directness	Plausible	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
DBS	use of ABR, SER, EEG frequency analysis	Poorly defined - regaining consciousness or some limited ability to communicate?	1 Class IV study Yamamoto 2010[e83]	The eight patients who recovered from VS showed desynchronization on continuous EEG frequency analysis. Sixteen (14.9%) of the 107 VS patients satisfied these								

				criteria, 10 of whom were treated with DBS and six of whom were not. In these 16 patients, the recovery rate from VS was different between the DBS therapy group and the no DBS therapy group ($P < 0.01$, Fisher's exact probability test)								
	Electrophysiologic inclusion criteria: 1. Vth wave of ABR recordable, N20 recordable, desyncrh pattern on cEEG freq anal, pain related P250 >7uV	Following instructions; "we devised a neurologic follow-up outcome scale for VS…" (Table 5)	1 Class III study Yamamoto 2013[e84]	21 patients with VS and 5 MCS patients treated with DBS. This almost certainly overlaps with study above as again, 8 of 21 patients recovered from VS and were able to follow verbal instructions. Compared patients who met electrophysiologic criteria (10/21 VS patients and 5/5 MCS patients) versus those who did not (11 VS, 0 MCS). Additionally, 6 patients in the non-DBS group met electrophysiologic	-	N/A	-	-	U?	N/A		

				criteria but family declined DBS. So for patients who received DBS, a positive electrophys profile was associated with an increased odds of recovery after DBS (8/10 vs 0/11 or 0.15/11.5, OR 88.0, 95% CI 5.4 to 1219.0; this goes more with response to treatment). For patients meeting electrophys criteria, 8/10 who received DBS recovered and 0/6 who did not recovered (or 0.5/6.5), for an OR of 48.0, 95% CI 2.9 to 679.9)								

Natural history evidence tables

Natural history at 3 months

OVERALL GP	Study		Key Prognostic Characteristics						Main Findings	Comment *Enter your summary conclusion here and any reason for upgrading or downgrading*	Confidence in Evidence	Exclude?	Additional Comments
	Author, Year	**Class**	**Time-post at enroll**	**Etiol**	**DOC Level**	**FUP**	**Outcomes**	**n**					
Time: 3mo Etiol: TR Pop: VS	Noe 2012 [e51]	III	Mean (whole gp)= 145 d (range=1-12 mo)	TR	VS	At least 6 months after enrollment or until emerged from MCS	Emergence from DoC via CRS-R	4 VS	*1/4 patient in TR VS transitioned to MCS at 2 months post injury.	1 Class III study tracked the transition from traumatic VS to emergence from MCS in 4 patients and found that 1/4 patients (25%: CI: 0-67.4% transitioned to MCS at 2 months post-injury (very low confidence).	Low when combined with Bagnato	No	

	Bagnato 2012 [e63]	III	1 mth post-injury	TR	VS (LCFS Level 1-2)	3 and 6m post-injury: n=53; 12m: n=36	Emergence from VS via LCFS	53 VS	By 3m: 18/53 (34% 95% CI: 21.2-46.7) emerged from VS to MCS, 35/53 (66% 95% CI: 53.3-78.8) remained VS	Combining Noe and Bagnato: 19/57 by 2-3 mo: 33% (22%-46%)	LOW (2 Class III studies)		
	Cavinato 2009 [e47]	III	5-12 weeks after head injury	TR	VS	12 m	Recovery of consciousness	34 patients	Recovery occurred earlier than 3 mo in 16 patients				
Time: 3mo Etiol: NT Pop: VS	Noe 2012 [e51]	III	Mean (whole gp)= 145 d (range=1-12 mo)	NT	VS	At least 6 months after enrollment or until emerged from MCS	Emergence from DoC via CRS-R	8 VS	Of the 8 patients admitted in NT VS, 0/8 emerged from MCS at 3 months per Joe's review, though I can't tell if the 1 person that	In a class III study which tracked outcome at 3m and included patients with nontraumatic VS, 0/8 patients (0%) had emerged from MCS at 3 months. (This is the	Very low	No-Study included but data for NT VS at 3m excluded from analysis.	Authors did not conduct systematic outcome assessment at a common time post-injury for eith the TR or NT VS subgroups. Subjects varied dramatically in length of time post-injury at enrollment (between

									emerged from VS+ MCS was TR or NT. Cannot, however, tell from the information provided whether the 3 patients who improved to MCS were TR or NT. Thus, not much information to use here.	only study on emergence in NT VS at 3 mo)			38-360 days) so no way to determine when outcome was actually assessed.
	Sazbon 1993 [e46]	III	30+ days post injury	NT	VS/Post-coma awareness	Follow-ups were conducted at different, unspecified times, up to 72m post-injury.	Death, recovery of consciousness, locomotion, ADLs, cognition, speech, employment	100	Among nTBI pts in VS for 1m, 15/100 (15.0%, CI: 8-22%) die within 3m.	The probability of death within 3m of injury in patients in nontraumatic VS for 1 month is 15.0% (CI: 8-22%, very low confide		No	

										nce, 1 class III study).			
	Mateen 2013 [e56]	III	>1 mo	NT	VS	Variable	Survival	18 NT (and one lost to FU)	At least 20/28 survived >3 mo (71%, 95% CI 53%-85%); 3 were followed >1 mo, 3 were followed >2 mo, and 2 died at 3 mo (so could be as much as 26/28, 93%, 95% CI 77%-98%)	If combine Sazbon (III) and Mateen (III), then at least 105/128 (82%, 95% CI 74%-88%)	Low		
Time: 3mo Etiol: TR Pop: MCS	Noe 2012 [e51]	III	Mean (whole gp)= 145 d (range=1-12 mo)	TR	MCS	At least 6 months after enrollment or until emerged from MCS	Emergence from DoC via CRS-R	11 MCS	2/11 patients (18.2%) admitted with traumatic MCS emerged by 3 months post admission (Ss	The probability of emergence from MCS at 3m post-injury is 18.2% (CI: 0-41%) in patients in traumatic	Very low	No-Study included but data for TR MCS at 3m excluded from analysis.	Authors did not conduct systematic outcome assessment at a common time post-injury for eith the TR or NT VS subgroups. Subjects varied dramatica

									who emerged from MCS were at 94 +/- 36.4 days post injury at admission)	MCS (n=11) and 15.0% (CI: 8-22%) in patients in nontraumatic MCS (n=9) (very low confidence, 1 class III study, downgrade for precision?).			lly in length of time post-injury at enrollment (between 38-360 days) so no way to determine when outcome was actually assessed.
Time: 3mo Etiol: NT Pop: MCS	Noe 2012 [e51]	III	Mean (whole gp)= 145 d (range=1-12 mo)	NT	MCS	At least 6 months after enrollment or until emerged from MCS	Emergence from DoC via CRS-R	9 MCS	2/9 patients in NT MCS emerged 2 months after admission (22.2%, CI:0-49.4%). The remaining 7/9 (77.8%, CI: 50.6-100%) cases remained in MCS through 6 mth ***post admission***, but note that Ss were between 38 and 360d post-injury at			No-Study included but data for NT MCS at 3m excluded from analysis.	Authors did not conduct systematic outcome assessment at a common time post-injury for eith the TR or NT VS subgroups. Subjects varied dramatically in length of time post-injury at enrollment (between 38-360 days) so no way to determine when outcome was actually assessed.

									time of admission.				

Natural history at 6 months

OVERALL GP	**Study**	**Key Prognostic Characteristics**							**Main Findings**	**Precision**	**Consistent**	**Directness**	**Plausible**	**Magnitude of Effect**	**Dose Response**	**Comment** *Enter your summary conclusion here and any reason for upgrading or downgrading*	**Confidence in Evidence**	**Additional Comments**	**Exclude?**
	Author, Year	**Class**	**Time-post at enroll**	**Etiol**	**DOC Level**	**FUP**	**Outcomes**	**n**											
Time: 6mo Etiol: TR Po	Sara 2011[e48]	III	Mean = 60 days	TR	VS	6 months after enrollment (8	Death, no change, GOSE	**19**	At 8m post-injury, 3/19 (15.8%, CI: 0-	D	-	-				Two class III studies involving			No

p: VS						m post-injury)			32.2) died; 9/19 (47.4%, CI: 24.9-69.8) remained in VS; 4/19 (21.1%, CI: 2.7-39.4) had partial disability (GOSE LS-LG) and 3/19 (15.8, CI: 0-32.2%) had full recovery (UG). 7/19 recovered out of VS: 37% (19%-					patients in traumatic VS tracked recovery of consciousness and death rates at 6m post-injury but two were excluded for methodologic reasons. One study failed to distinguish VS and MCS pati			

									59 %)					ents at baseline or at time of outcome assessment and did not control for length of time post-injury (ie, 2-12 months). A second study that tracked the transition from VS to emergence from			
	Noe 2012[e51]	III	mean=145 days (range=1-12 months)	TR	VS	At least 6 months after enrollment or until emerged from MCS	Emergence from DoC via CRS-R	4	0/3 (0%) of Ss still in VS with TBI at 3m post admission emerged between 3-6 months post admission, although injury to admission varied (1-12 months). It is unclear how many transitio							Authors did not conduct systematic outcome assessment at a common time post-injury for eith the TR or NT VS subgroups. Subjects varied dramatically in length of time post-injury at enrollment (between 38-360 days) so no way to determine when outcome was actually assessed.	No-Study included but data for TRVS excluded from analysis.

									ned to MCS (see table 1).							MCS included fewer than 5 patients and did not control for length of time post-injury (ie, 1-12 months) at time of follow-up.						
	Bagnato 2012[e63]	III	1 mth post-injury	TR	VS (LCFS Level 1-2)	3 and 6 m post-injury: n=53; 12 m: n=36	Emergence from VS via LCFS	53 VS	By 6m: 35/53 (66% 95% CI: 53.3-78.8) emerged from VS to	-	-	-					Bagnato + Sara = very low, downgrade for precision					

									MCS, 18/53 (34% 95% CI: 21.2-46.7) remained VS								, see meta-analysis						
	Cavinato 2009[e47]	III	5-12 weeks after head injury	TR	VS	12 m	Recovery of consciousness	34 patients	Recovery occurred earlier in 8 patients 3-6 months, for a total of 24 by 6 mo (24/34, 71%, 95% CI 54%-83%)															
Time: 6 mo Etiol: NT	Sara 2011[e48]	III	Mean = 60 days	NT	VS	6 months after enrollment	Death, no change, GOSE	**19**	At 8m post-injury, 11/19 (57.9%,	D	-	-											No

Pop: VS						(8 m post-injury)			CI: 35.7 - 80.1) died ; 2/19 (10.5%, CI: 0- 24.3) remained in VS and 6/19 (31.6%, CI: 10.7 - 52.5) had partial disability (GOSE LS-LG) .										
	Sazbon 1993[e46]	III	30 + days post injury	NT	VS/ Post-coma awareness	Follow-ups were conducted at different, unspecifiedti	Death, recovery of consciousness, locomotion, ADLs, cognition, speech	100	20/100 Ss recovered consciousnss prior to 6m post-injury (20%, CI: 12.2%-	-	-	-				Among patients who remain in non traumatic VS for at least one mo			No

						mes, up to 72 m po st-inj ur y.	, em plo ym ent		27.8 %); 49/100 (49 %, CI: 39.2 - 58.8 %) who wer e still in VS at 6m post - inju ry rem aine d unc ons ciou s unti l deat h and 31/99 (CI: 21.9 - 41 %) died with in 12m .							nth , at 6 mt hs pos t- inj ury , the pro bab ilit y of dea th is 31 % (CI : 21. 9- 40. 1%), per sist ent VS 49 % (CI : 39. 2- 58. 8%) and rec ove ry of con sci ous nes s 20 % (CI : 12. 2- 27. 8%).			

																(low confidence, one class III study).			
	Noe 2012[e51]	III	mean=145 days (range=1-12 months)	NT	VS	At least 6 months after enrollment or until emerged from MCS	Emergence from DoC via CRS-R	8	0/8 (0%) of NT VSs emerged from MCS between 2m and 16m post-injury; Unclear how many transitioned to MCS (see table 1).							NOT ENOUGH INFO TO INCLUDE		Authors did not conduct systematic outcome assessment at a common time post-injury for eith the TR or NT VS subgroups. Subjects varied dramatically in length of time post-injury at enrollment (between 38-360 days) so no way to determine when outcome was actually assessed.	No-Study included but data for NT VS at 6m excluded from analysis.
	Tsubokawa 1990[e57]	III	2-12 mths	NT	"Prolonged coma"	At least 8 months post-inj	PCS	25	Died=6 (19%), VS=19 (61%), Recovered							NOT ENOUGH INFO TO INCL	Very Low	VS and MCS cannot be distinguished at baseline (ie all Ss reportedly in "prolonged coma"; VS group includes Ss able to take food by mouth and track objects) and time of outcome	YES (Other)

						ury			consciousness=3 (10%), Unaccounted for=3 (10%). See comment.							UDE		assessment cannot be determined (Ss enrolled between 2-12m post-injury and assessed 6m later but no way to tell when each S was assessed. Also, authors report that 6 Ss died but table 3 shows outcomes for all 31 Ss, none of which include death.				
	Mateeen 2013[e56]	III	>1 mo	NT	VS	Variable	Survival	18 NT (and one lost to FU)	At least 17/28 survived >6 mo (61%, 95% CI 42%-76%); could be as much as 26/28 because only 2 known to have died (93%, 95% CI 77								Low					

									%-98 %)												
	Estraneo 2013[e62]	III	1-6 mths	NT	VS	6-24 mths post-injury	Responsive: MCS; Fully conscious: EMCS	43	3/43 (7% 95% CI: 0-14.6) emerged from VS to MCS by 6m	-	-	-						Authors do not report how many patients remained VS v. died by 6m.				
Time: 6mo Etiol: NT Pop: MCS	Noe 2012[e51]	III	mean=145 days (range=1-12 months)	NT	MCS	At least 6 months after enrollment or until emerged from MCS	Emergence from DoC via CRS-R	9	0/7 nTBI MCS subjects emerged from MCS between 3-6 months post admission (2 of the 9 patients in the cohort had eme	D	-	-				Patients who remain in non traumatic MCS for more than two months are not likely to emerge from M	Very low	Authors did not conduct systematic outcome assessment at a common time post-injury for eith the TR or NT VS subgroups. Subjects varied dramatically in length of time post-injury at enrollment (between 38-360 days) so no way to determine when outcome was actually assessed.				No-Study included but data for NT MCS at 6m excluded from analysis.

									rged at 2 months post admission).							CS by 6 months post-injury. One class III study reported that of 9 patients who remained in MCS for at least 2 months, 0/7 emerged between 3 and 6 months post-admissio			

																n (very low confidence, 1 class III study, downgraded for precision?).			
Time: 6 mo Etiol: TR Pop: MCS	Noe 2012[e51]	III	mean=145 days (range=1-12 months)	TR	MCS	At least 6 months after enrollment or until emerged from MCS	Emergence from DoC via CRS-R	11	5/11 (45.5%, CI: 16.0-74.9%) MCS Ss with TBI emerged by 7 months (between 2- and 6-mo follow-ups). 5/11 (45.5%) traumatic MCS Ss emerged	D	-	-				Patients who remain in traumatic MCS for more than two months have a 45% likelihood of emerging from M	Very low	Authors did not conduct systematic outcome assessment at a common time post-injury for eith the TR or NT VS subgroups. Subjects varied dramatically in length of time post-injury at enrollment (between 38-360 days) so no way to determine when outcome was actually assessed.	No-Study included but data for TR MCS at 6 m excluded from analysis.

									by 6 months post admission, although time from injury to admission varied.)							CS by 7 months post-injury (CI: 16.0-74.9%, very low confidence, 1 class III study, downgraded for precision?)				

Natural history at 12 months

OVERALL GP	Study	Key Prognostic Characteristics							Main Findings										
	Author, Year	**Class**	**Time-post at enroll**	**Etiol**	**DOC Level**	**FUP**	**Outcomes**	**n**		**Precision**	**Consistent**	**Directness**	**Plausible**	**Magnitude of Effect**	**Dose Response**	**Comment** *Enter your summary conclusion here and any*	**Confidence in Evidence**	**Additional Comments**	**Exclude?**

																reason for upgrading or downgrading			
Time: 12mo Etiol: NT Pop: VS	Sazbon 1993[e46]	III	30+ days post injury	NT	VS	Follow-ups were conducted at 1, 3, 6, 9, 12, 18, 24, 30, 36, 48 and 72m post-injury.	Death, recovery of consciousness, locomotion, ADLs, cognition, speech, employment	100	Among 100 Ss in NT VS for at least 4 weeks, 46/99 (46.5%, CI: 36.6 - 56.3, 1 lost to f/u) died by 12m post-injury, and of the 49 Ss still in VS at 6m post-injury, none recovered consciousness	-	-	-				The probability of death at 12m post-injury in patients in NT VS for at least 4 weeks is 46% (CI: 36.6 - 56%). The probability of recovery of consciousness in those who remain in NT VS for 6m is nil (very low	Very low		No

									prior to death.							confidence, one class III study).			
	Noe 2012[e51]	III	mean= 145 days (range=1-12 months)	NT	VS	At least 6 months after enrollment or until emerged from MCS	Emergence from MCS via CRS-R	8	Noe: Of 4 Ss originally in TRVS and 8 Ss originally in NTVS, 9/12 remained in VS at last f/u (75%, CI: 50.5%-95.5%). Time of f/u not explicitly stated but appears to be at least 12 mo post injury. 2 transitioned to MC	D	-	D				In one class III study that followed 8 patients who were in nontraumatic VS for 1-12m, none went on to emerge from MCS at time of last f/u conducted at a mean of 16m post-injury).		Authors did not conduct systematic outcome assessment at a common time post-injury for either the TR or NTVS subgroups. Subjects varied dramatically in length of time post-injury at enrollme	No

									S (16.7%, CI: 0-37.8%) but not stated when these 2 emerged from VS. Both remained in MCS at last f/u more than 12mths post-injury. None of 11 Ss (3 TRVS and 3 NTVS) who remained in either VS or MCS for at least 6 mo post injury									nt (between 38-360 days) so no way to determine when outcome was actually assessed.	

									emerged from MCS.; Estraneo: 6/43 (14% 95% CI: 3.6-24.3) emerged from VS to MCS by 12m										
	Estraneo 2013[e62]		1-6 mths	NT	VS	6-24 mths post-injury	Responsive: MCS; Fully conscious: EMCS	43	Estraneo: 6/43 (14% 95% CI: 3.6-24.3) emerged from VS to MCS by 12m	-	-	-				Authors do not report how many patients remained VS vs died by 12 mo.		
	Mateeen 2013[e56]	III	>1 mo	NT	VS	Variable	Survival	18 NT (and one lost to FU)	At least 12/28 survived >12 mo (43%, 95% CI 27%-61%), but								Low		

									only 3 known to have died, so could be as high as 25/28 (89%, 95% CI 73%-96%)										
Time: 12 mo Etiol: TR Pop: VS	Noe 2012[e51]	III	mean=145 days (range=1-12 months)	TR	VS	At least 6 months after enrollment or until emerged from MCS	Emergence from MCS via CRS-R	4								In one class III study that followed 4 patients who were in traumatic VS for 1-12m, of the 3 who remained in either VS or MCS at 6 months, none	Low		No

																went on to emerge from MCS at time of last f/u conducted at a mean of 16 mo post injury.			
	Danze 1994[e52]	III	1 mo	TR	VS	12m post-injury	GOS	522	Death: 19.3% (95% CI: 16-22.7); VS: 19.7% (95% CI: 16.3-23.1); SD: 46.7% (95% CI: 42.5-51); MD+GR: 14.% (95% CI: 11.2-	-	-	D				Study conducted prior to release of definition and diagnostic criteria for MCS (ie, sample may have included patients in MCS by current standards).	Low		No

									17.2).										
	Sazbon 1990[e53] and Grosswasser 1990[e68]	III	Coma > 30 days	TR	VS ("prolonged unawareness state")	12 months post-injury	Recovery of consciousness defined as 1st instance of "meaningful communicative contact with environment by either motor, visual or verbal act."	134	12-month outcome: Recovery of consciousness in 72 of 134 or 53.7% (CI: 45.3 - 62.2), most reportedly in the 2nd or 3rd month post-injury. 43 of 62 (69.3%, 95% CI: 57.9 - 80.8) who remained in	-	-	D				Study conducted prior to release of definition and diagnostic criteria for MCS (ie sample may have included patients in MCS by current standards).	Low		No

									VS died by 12m (mean time to death = 15.5 +/- 21.6 m).										
	Cavinato 2009[e47]	III	1-3 mo	TR	VS	NPVS (DRS>22: pts who had recovered consciousness or in MCS)= 54 +/- 23 days (range=49–82)...PVS 58 +/- 21 days (range=52–84)	DRS and PVS (DRS<22) v. NPVS (ie, pts who had recovered consciousness or in MCS DRS >22).	34	26/34 (76.5%, CI: 62.2 - 90.7%) recovered consciousness by 12m (16[47%] <3m, 8[24%] between 3-6m, and 2[6%] >6m). DRS at 12m: Ext VS= 4 (11.8%, CI: 1-22.6%); VS=	-	-	-				The probability of recovery of consciousness by 12m in patients who remain in TRVS for 1-3m is 76.5% (CI: 62.2 - 90.7%). Among this group, at 12m post-injury, the probability of extreme	Very low		No

									4 (11.8%, CI: 1-22.6%); Ext Sev = 14 (41.2%, CI: 24.6-57.7%) SD=9 (26.5%, CI: 11.6-41.3%), Mod-Sev =3 (8.8%, CI: 0-18.4), GR= 0%.							VS is 11.8% (CI: 1-22.6%), extremely severe disability 41.2%, (CI: 24.6-57.7%), severe disability 26.5% (CI: 11.6-41.3%), moderately severe disability 8.8% (CI: 0-18.4) and good recovery 0 (very low confidence, 1 class III			

																study, downgraded for precision?).			
	Bagnato 2012[e63]		1 mo post injury	TR	VS (LCFS Level 1-2)	3 and 6m post-injury: n=53; 12m: n=36	Emergence from VS via LCFS	53 VS	By 12m: 28/36 (77.8% 95% CI: 64.2-91.4) emerged from VS to MCS, 8/36 (22.2% 95% CI: 8.6-35.8) remained VS.	D?	-	-							
Time: 12 mo Etiol: TR Pop: MCS	Noe 2012[e51]	III	mean=145 days (range=1-12 months)	TR	MCS	At least 6 months after enrollment or until emerged from MCS	Emergence from MCS via CRS-R	11	In one Class III study that followed 11 patients who were in traumatic MC	D	-	-				In one Class III study that followed 11 patients who were in traumatic MC	Very low	Authors did not conduct systematic outcome assessment at a common time post	No

									S for 1-12m, of the 6 who remained in MCS at 6m post admission, none showed further recovery when reassessed at a mean of 489 days (+/-184.1) post-injury.							S for 1-12m, of the 6 who remained in MCS at 6m post admission, none showed further recovery when reassessed at a mean of 489 days (+/-184.1) post-injury (very low confidence, one class III study, downgrade for precision?).		- injury for either the TR or NT MCS sub groups. Subjects varied dramatically in length of time post-injury at enrollment (between 38-360 days) so no way to determine when outcome was actually asse	

Time: 12 mo Etiol: NT Pop: MCS	Noe 2012[e51]	III	mean=145 days (range=1-12 months)	NT	MCS	At least 6 months after enrollment or until emerged from MCS	Emergence from MCS via CRS-R	9	In 1 class III study that followed 9 patients who were in nontraumatic MCS for 1-12m, of the 7 who remained in MCS at 6m, none showed further recovery when reassessed at a mean of 489 days (+/-184.1) post injury.	D	-	-				In 1 class III study that followed 9 patients who were in traumatic MCS for 1-12m, of the 7 who remained in MCS at 6m post admission, none showed further recovery when reassessed at a mean of 489 days (+/-184.1) post-injury.	Very low	ssed. Note also that the last f/u (ie 489 +/-184) would have occurred anywhere between 16m and 30m post-injury.	No

Natural history at 24 months

OVERALL GP	Study	Key Prognostic Characteristics							Main Findings									
	Author, Year	Class	Time-post at enroll	Etiol	DOC Level	FUP	Outcomes	n		Precision	Consistent	Directness	Plausible	Magnitude of Effect	Dose Response	Comment *Enter your summary conclusion here and any reason for upgrading or downgrading*	Confidence in Evidence	Exclude?
Time: 24mo Etiol: Mixed (TR+NT) Pop: VS	Luaute 2010[e49]	II	12 m+	TR	VS	2, 3, 4, and 5 yrs post-injury	Death, VS,MCS, PTCS, GOS	2	VS Y2 post-injury: Died: 4/11 (36.4 %, CI: 7.9-64.8); VS: 7/11 (63.6 %, CI: 35.2-92.1).	D	-	-				No etiologic breakdown available		No (Mixed)
	Luaute 2010[e49]	II	12 m+	NT	VS	2, 3, 4, and 5 yrs post-injury	Death, VS,MCS, PTCS, GOS	10		D	-	-				No etiologic breakdown available		No (Mixed)
Time: 24mo Etiol: Mixed (TR+NT) Pop: MCS	Luaute 2010[e49]	II	12 m+	TR	MCS	2, 3, 4, and 5 yrs post-injury	Death, VS,MCS, PTCS, GOS	16	MCS overall: Died: 14/39 (35.9 %, CI: 20.8-51.0); Remained MCS: 9/39 (23.1 %,	D	-	-				No etiologic breakdown available		No (Mixed)
	Luaute 2010[e49]	II	12 m+	NT	MCS	2, 3, 4, and 5 yrs post-	Death, VS,MCS, PTCS, GOS	23		D	-	-				No etiologic breakdown available		No (Mixed)

						injury			CI: 9.9-36.3), Emerged from MCS (PTCS): 13/39 (33.3%, CI: 18.5-48.1); 3 (8%) lost to follow-up.									
Time: 24mo Etiol: NT Pop: VS	Sazbon 1993[e46]	III	30 days+	NT	VS	Follow-ups were conducted at 1, 3, 6, 9, 12, 18, 24, 30, 36, 48 and 72m post-injury	Death, recovery of consciousness, locomotion, ADLs, cognition, speech, employment	100	No change from 6 month follow up in consciousness; 59/99 (56.6%, CI: 49.9-69.3%) died within 24m (1 lost to f/u).	-	-	-				The probability of death by 24m post-injury in patients in NT VS for at least 4 weeks is 56.6% (CI: 49.9-69.3%). Of 41 patients still alive at 24 months post-injury, none of those		No

																who were still in VS at 6 months recovered consciousness between 6 and 24 months. Thus, the probability of recovery of consciousness in those who remain in NT VS for 6m is nil (very low confidence, one class III study).		
	Estraneo 2013[e62]		1-6 mths	NT	VS	6-24 mths post-injury	Responsive: MCS; Fully conscious: EMCS	43	By 24m: 9/43 (20.9% 95% CI: 8.8-33.1) emerged from VS to MCS,	D?	D	-				Re Precision, wide Cis; Re Consistency, Estraneo more favorable		

									12/43 (27.9 % 95% CI: 14.5-41.3) remained VS and 22/43 (52.2 % 95% CI: 36.2-66.1) died. Authors don't report at what specific time point patients transitioned from VS to MCS or died prior to 24m.							than Szabon.		
	Mateen 2013[e56]	III	>1 mo	NT	VS	Variable	Survival	18 NT (and one lost to FU)	At least 8/28 survived >24 mo (29%, 95% CI 15%-47%), but only 4 known to have died,								Low	

									so could be as high as 24/28 (86%, 95% CI 69%-94%)										

Natural history at greater than 24 months

OVERALL GP	Study	Key Prognostic Characteristics							Main Findings										
	Author, Year	Class	Time-post at enroll	Etiol	DOC Level	FUP	Outcomes	n		Precision	Consistent	Directness	Plausible	Magnitude of Effect	Dose Response	Comment *Enter your summary conclusion here and any reason for upgrading or downgrading*	Confidence in Evidence	Exclude?
Time: >24 mo Etiol: TR Pop: VS	Mateen 2013[e56]	II	>1 mo	TR	VS	Variable (years)	Survival	n=7 for TR	7 TR VS lived for 4 years, 12 years, >1 month, >5.5 years, >4 years, >3 years, >1 month At least	D					NA		Very low	

									5/7 lived >24 months: 71% (36%-92%); other 2 were only observed >1 mo									
Time: >24 mo Etiol: Mixed (TR+NT) Pop: VS	Luaute 2010[e49]	II	12 m+	TR+NT	VS	2, 3, 4, and 5 y post injury	Death, VS,MCS, PTCS, GOS	12	No breakdown by etiology: Cumulative frequencies: YR3: Death= 5/11 (45.5%, CI: 16.0-74.9), VS= 1/11 (9.1%, CI: 0-26.1); MCS=0%; YR4: Death= 6/11 (54.5%, CI: 25.1-84.0),	D	-	-				Sample was not analyzed separately by etiology.		No (Mixed)

									VS= 1/11 (9.1 %, CI: 0-26.1); MCS =0%; YR5: Death= 9/11 (81.8 %, CI: 59.0-1.00), VS= 3/11 (27.3 %, CI: 0.1-53.6), MCS : 0%; Lost =1									
Time: >24 mo Etiol: TR Pop: Mixed (VS+MCS)	Skansden 2008[e50]	II	3 years	TR	VS/MCS	3-8 y post injury (median=62m; range=36-95)	GOSE, Return to work/school	Total =87: VS/MCS =25; PTCS=23; Oriented =34; Lost =5 (surviving at 3 years	***No breakdown by diagnosis: Mixed VS/MCS: VS= 3/25 (12.0 %, CI: 0-24.7), LS=13/25 (52%, CI: 32.4-71.6); US=	-	-	?				Sample was not analyzed separately by dx (VS and MCS mixed). GOSE scores were obtained via interview anytime betw		No

									1/25 (4%, CI: 0-11.7); LM= 6/25 (24%, CI: 7.3-40.7, UM= 1/25 (4%, CI: 0-11.7); LG= 0, UG= 0; Median GOSE = 3 for VS/ MCS; Productivity (%) (age 7-64): Mixed VS/ MCS: Work=0, Disabled = 19/24 (79.2%, CI: 62.9-95.4), Normal Student=							een 3 and 8 y post injury. No data showing when Ss were assessed so results need to be discussed as occurring between 3 and 8 y post injury.		

									0, Adj Student= 4/24 (16.7 %, CI: 1.8-31.6), Other= 1/24 (4.2 %, CI: 0-12.2).									
Time: >24 mo Etiol: NT Pop: VS	Sazbon 1993[e46]	III	30 days+	NT	VS	Follow-ups were conducted at 1, 3, 6, 9, 12, 18, 24, 30, 36, 48 and 72m post-injury	Death, recovery of consciousness, locomotion, ADLs, cognition, speech, employment	100	36 Months:60/98 dead (61.2 %, CI:51.6-70.9 %, Lost-2). 48 months: 64/96 dead (66.7 %, CI: 57.2-76.1 %, Lost-4). 72 Months 68/95 dead (71.6 %, CI: 62.5-80.6 %, Lost-	-	-	-				Among patients who remain in nontraumatic VS for at least one mo, the probability of death is 61.2 % (CI: 51.6-70.9 %) at 36 mo post-injury, 66.7 %, (CI: 57.2-76.1 %) at 48 mo		No

									5)… Of the 18 for whom follow up data were available regarding occupational placement, only one was gainfully employed, while three were in sheltered day-placement conditions and 14 were in round-the-clock nursing care.							post, and 71.6% (CI: 62.5-80.6%) at 72 mo post (very low confidence, one Class III study).		
	Mateeen 2013[e56]	III	>1 mo	NT	VS	Variable	Survival	18 NT (and one lost to FU)	At least 8/28 survived >24 mo (29%, 95% CI								Low	

									15%-47%), but only 4 known to have died, so could be as high as 24/28 (86%, 95% CI 69%-94%)									
Time: >24 mo Etiol: Mixed (TR+NT) Pop: MCS	Luate 2010[e49]	II	12 m+	TR+NT	MCS	2, 3, 4, and 5 y post-injury	Death, VS,MCS, PTCS, GOS	39	No breakdown by etiology: Cumulative frequencies: YR3: Dead=10/36 (27.8%, CI: 13.1-42.4), VS=0, MCS=18/36 (50.0%, CI:33.7-66.3), SD=11/36 (30.6	D	-	-				Sample was not analyzed separately by etiology.		No (Mixed)

									%, CI: 15.5-45.6); YR4: Dead=15/36 (41.7%, CI: 25.6-57.8), VS=0, MCS=10/36 (27.8%, CI: 13.1-42.4), SD=13/36 (36.1%, CI: 20.4-51.8); YR5: Dead=15/36 (41.7%, CI: 25.6-57.8), VS=0, MCS=9/36 (25.0%, CI: 10.9-39.1), SD=13/36 (36.1									

									%, CI: 20.4-51.8); Lost =3.									

Appendix e-9. Steps and rules for formulating recommendations

Constructing the recommendation and its rationale

Rationale for recommendation summarized in the rationale includes 3 categories of premises

- Evidence-based conclusions for the systematic review
- Stipulated axiomatic principles of care
- Strong evidence from related conditions not systematically reviewed

Actionable recommendations include the following mandatory elements

- The patient population that is the subject of the recommendation
- The person performing the action of the recommendation statement
- The specific action to be performed
- The expected outcome to be attained

Assigning a level of obligation

Modal modifiers used to indicate the final level of obligation (LOO)

- Level A: *Must*
- Level B: *Should*
- Level C: *May*
- Level U: No recommendation supported

LOO assigned by eliciting panel members' judgments regarding multiple domains, using a modified Delphi process. Goal is to attain consensus after a maximum of 3 rounds of voting. Consensus is defined by:

- $\geq$ 80% agreement on dichotomous judgments
- $\geq$80% agreement, within 1 point for ordinal judgments
- If consensus obtained, LOO assigned at the median. If not obtained, LOO assigned at the 10^{th} percentile

Three steps used to assign final LOO

1. Initial LOO determined by the cogency of the deductive inference supporting the recommendation on the basis of ratings within 4 domains. Initial LOO anchored to lowest LOO supported by any domain.
    - Confidence in evidence. LOO anchored to confidence in evidence determined by modified form of the Grading of Recommendations Assessment, Development and Evaluation process
        - Level A: High confidence
        - Level B: Moderate confidence
        - Level C: Low confidence
        - Level U: Very low confidence

- Soundness of inference assuming all premises are true. LOO anchored to proportion of panel members convinced of soundness of the inference
    - Level A: 100%
    - Level B: ≥ 80% to < 100%
    - Level C: ≥ 50% to < 80%
    - Level U or R: < 50%
- Acceptance of axiomatic principles: LOO anchored to proportion of panel members who accept principles
    - Level A: 100%
    - Level B: ≥ 80% to < 100%
    - Level C: ≥ 50% to < 80%
    - Level U or R: < 50%
- Belief that evidence cited from rerated conditions is strong: LOO anchored to proportion of panel members who believe the related evidence is strong
    - Level B: ≥ 80% to 100% (recommendations dependent on inferences from nonsystematically reviewed evidence cannot be anchored to a Level A LOO)
    - Level C: ≥ 50% to < 80%
    - Level U or R: < 50%

2. LOO is modified mandatorily on the basis of the judged magnitude of benefit relative to harm expected to be derived from complying with the recommendation
    - Magnitude relative to harm rated on 4-point ordinal scale
        - Large benefit relative to harm: benefit judged large, harm judged none
        - Moderate benefit relative to harm: benefit judged large, harm judged minimal; or benefit judged moderate, harm judged none
        - Small benefit relative to harm: benefit judged large, harm judged moderate; or benefit judged moderate, harm judged minimal; or benefit judged small, harm judged none
        - Benefit to harm judged too close to call: benefit and harm judged to be substantially similar
    - Regardless of cogency of the recommendation the LOO can be no higher than that supported by the rating of the magnitude of benefit relative to harm
        - Level A: large benefit relative to harm
        - Level B: moderate benefit relative to harm
        - Level C: small benefit relative to harm
        - Level U: too close to call
    - LOO can be increased by one grade if LOO corresponding to benefit relative to harm greater than LOO corresponding to the cogency of the recommendation

3. LOO optionally downgraded on the basis of the following domains

- Importance of the outcome: critical, important, mildly important, not important
- Expected variation in patient preferences: none, minimal, moderate, large
- Financial burden relative to benefit expected: none, minimal, moderate, large
- Availability of intervention: universal, usually, sometimes, limited

Appendix e-10. Rationale of factors considered in developing the practice recommendations

In this appendix, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based. Please see appendix e-9 for the steps and rules for formulating recommendation strength.

PRACTICE RECOMMENDATIONS

Unless otherwise noted, all recommendations specifically apply to the population addressed in this guideline (individuals with prolonged DoC [i.e., ≥28 days]).

Recommendation 1

Rationale for recommendation 1

Our systematic review has highlighted the complexities of caring for patients with a prolonged DoC (i.e., ≥28 days) at every stage, including diagnosis, prognosis, and treatment (EVID). Such patients may be misdiagnosed due to confounding neurologic deficits (RELA)[e20] or inexperience in examining patients for subtle signs of consciousness (RELA.)[e87] Accurate diagnosis is important to educate families about patients' level of consciousness and function, to inform prognostic counseling, and to guide treatment decisions (PRIN). Knowledge gaps often lead to over- or under-estimation of prognosis by nonspecialists (RELA)[e88] In addition, patients with prolonged DoC frequently experience significant medical complications that can slow recovery and interfere with treatment interventions (RELA).[e89] 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 (PRIN). This is supported by findings from TBI, where cumulative mortality at 3-years post discharge is significantly lower for patients discharged to home or rehabilitation facilities than those discharged to skilled nursing, even after adjusting for confounders (RELA).[e90] In the context of these diagnostic, prognostic, and treatment considerations, care for patients with prolonged DoC may benefit from a team of multidisciplinary DoC rehabilitation specialists, which may include neurologists, psychologists, neuropsychologists, physiatrists, physical therapists, occupational therapists, speech pathologists, nurses, nutritionists, internists, and social workers.

Recommendation statement 1

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

Rationale profile for recommendation 1

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 5	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 1	Modest 3	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 5	Usually 7	Always 1	Yes
Cost relative to net benefit	Very large 0	Large 2	Moderate 8	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 2

Rationale for all of recommendation 2

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 (PRIN). Interpretation of inconsistent behaviors or simple motor responses are particularly challenging (PRIN). Fluctuations in arousal and response to command further confound the reliability of clinical assessment (RELA).[e91,e92] Underlying central and peripheral impairments such as aphasia,

neuromuscular abnormalities, and sensory deficits may also mask conscious awareness (RELA).[e93-e95] Clinician reliance on nonstandardized procedures, even when the examination is performed by experienced clinicians (RELA),[e18-e20] contributes to diagnostic error, which consistently hovers around 40%. Diagnostic error also includes misdiagnosing the locked-in syndrome (a condition in which full consciousness is retained) for VS/UWS and MCS (RELA).[e96,e97] Accurate diagnosis of the level of consciousness is important because of its implications for prognosis and management (PRIN).

Additional rationale for recommendation 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 (RELA).[e18,e98] The validity and reliability of standardized neurobehavioral assessment scales for diagnosis of DoC subtype have been previously reviewed (RELA).[e22] Other techniques such as Individualized Quantitative Behavioral Assessment have been useful in distinguishing specific purposeful responses from generalized, nonpurposeful, or reflexive responses (RELA).[e99] 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 (INFER). If standardized assessments are used, those with the highest quality of evidence should be employed (PRIN). A systematic review performed by the ACRM (RELA) recommended the CRS-R,[e98] Wessex Head Injury Matrix,[e100] Sensory Modality Assessment and Rehabilitation Technique,[e101] Western NeuroSensory Stimulation Protocol,[e102] the DOCS,[e58] and the Sensory Stimulation Assessment Measure[e103] for use in clinical practice (with varying levels of confidence across measures).[e22]

Recommendation statement 2a

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

Rationale profile for recommendation 2a

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 10	Yes
Variation in preferences	Large 0	Moderate 2	Modest 1	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 2	Usually 7	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 8	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Additional rationale for recommendation 2b, serial evaluations

While there is insufficient high-quality evidence to recommend the use of serial evaluations to improve the diagnostic sensitivity and specificity among DoCs (EVID), 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 greater risk of misdiagnosis (PRIN). Multiple behavioral evaluations over time may improve diagnostic reliability and accuracy as compared with a single evaluation (PRIN, INFER). Serial evaluations conducted by trained clinician(s) using a standardized, validated neurobehavioral assessment instrument have the potential to improve the reliability/validity of the diagnosis (INFER). There are insufficient data to recommend a minimum duration of time for an assessment session or how often serial examinations should be performed (EVID). 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 (PRIN).

Recommendation statement 2b

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

Rationale profile for recommendation 2b

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 0	Very important 4	Critically important 10	Yes
Variation in preferences	Large 0	Moderate 2	Modest 1	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 2	Usually 7	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 8	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Additional rationale for recommendation 2c, 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) (PRIN). The level of consciousness cannot be assessed accurately during periods of low arousal (PRIN). 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 (PRIN). Identifying and treating conditions that impair neurologic functioning may also improve arousal and level of consciousness (PRIN).

Recommendation statement 2c

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

Rationale profile for recommendation 2c

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 0	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 6	Critically 7	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 1	Usually 2	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 2d

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

Rationale profile for recommendation 2d

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 4	Critically 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 6	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 7	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Additional rationale for recommendation 2e, 2f, use of multimodal evaluations in VS/UWS

This systematic review identified that some electrophysiologic procedures (specifically, EMG thresholds for detecting response to motor commands, EEG reactivity, LEP responses, and the TMS-induced PCI) possibly have value for distinguishing MCS from VS/UWS, generally to an only mildly important degree (EVID). There is currently insufficient evidence to support or refute the routine clinical use of functional neuroimaging (fMRI or PET) or routine EEG or ERP studies as clinically useful adjuncts to behavioral evaluations to detect conscious awareness in patients diagnosed with VS/UWS (EVID). Additionally, functional imaging is not widely available and may not be clinically feasible in large numbers of patients (PRIN). However, 2 reviewed studies[e36,e40] 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%, 95% CI 14%–69%, and 38%, 95% CI 23%–56%, respectively) (EVID). 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 1 study of patients with VS/UWS based on standardized neurobehavioral assessment, functional neuroimaging studies (i.e., ^{18}F-FDG PET, active fMRI) performed at various times post injury (from < 1 month post insult to > 1 year post insult) demonstrated evidence of brain activity compatible with at least minimal conscious awareness in

approximately 32% of patients scanned using ^{18}F-FDG PET or mental imagery MRI or both (13/41, 95% CI 20%–47%), with ^{18}F-FDG PET showing results consistent with MCS in 33% of patients diagnosed with VS/UWS by the CRS-R (12/36, 95% CI 20%–50%) and mental imagery fMRI showing results consistent with MCS in 11% (3/28; 95% CI 4%–27%) (RELA).[e44] 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%, 95% CI 24%–45%) were classified as suggestive of MCS, with a greater recovery of consciousness in those categorized as MCS than VS/UWS on the EEG (11/50 VS vs 11/23 MCS, with 2 lost to follow-up; risk difference 26%, 95% CI 3%–47%) (RELA).[e104]

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 above) (RELA), and the exact link between these findings and consciousness remains unclear (PRIN). Thus, widespread use of multimodal imaging is unlikely to change the diagnosis in most patients diagnosed with VS/UWS (INFER). At the same time, injury sequelae (such as severe hypertonus) may confound behavioral assessment and compromise diagnostic accuracy (PRIN). 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%) of cases (RELA).[e44]

Recommendation statement 2e

In situations where there is continued ambiguity regarding evidence of conscious awareness despite serial neurobehavioral assessments, or where confounds 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).

Rationale profile for recommendation 2e

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 2	Benefit > harm 2	Benefit >> harm 6	Benefit >>> harm 4	No
Importance of outcomes	Not important or unknown 1	Mildly Important 1	Very important 9	Critically important 3	Yes
Variation in preferences	Large 1	Moderate 1	Modest 8	Minimal 4	Yes
Feasible	Rarely 2	Occasionally 9	Usually 3	Always 0	Yes
Cost relative to net benefit	Very large 4	Large 7	Moderate 2	Small 1	No
Strength of recommendation	R/U	C	B	A	

Recommendation statement 2f

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

Rationale profile for recommendation 2f, part I (identifying signs of conscious awareness)
*Strength of inference and strength of recommendation**

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 6	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 2	Modest 2	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 4	Usually 6	Always 4	No
Cost relative to net benefit	Very large 1	Large 1	Moderate 7	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

*Most voting anchored at Level B, but because of the lack of consensus on feasibility, the final recommendation was Level C.

Rationale profile 2f, part II (decisions regarding intensity of rehabilitation treatment)
Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 1	Benefit >> harm 8	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 1	Mildly Important 0	Very important 11	Critically important 2	Yes
Variation in preferences	Large 2	Moderate 1	Modest 1	Minimal 10	No
Feasible	Rarely 0	Occasionally 4	Usually 8	Always 2	Yes
Cost relative to net benefit	Very large 1	Large 5	Moderate 5	Small 3	No
Strength of recommendation	R/U	C	B	A	

Recommendation 3

Rationale for recommendation 3

In patients with severe TBI, many of whom have a DoC, 1 study found that hospital mortality was 31.7% (95% CI 28.4%–35.2%), with 70.2% (95% CI 63.9%–75.7%) of those deaths associated with the withdrawal of life-sustaining therapy (RELA).[e88] 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 GCS motor score (RELA).[e88] While withdrawal of life-sustaining therapy in this TBI population was high, this systematic review identified that individuals with a DoC lasting longer than 1 month post injury may still attain functionally significant recovery after 1 year post injury (EVID). 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 (RELA). For example, 1 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 or more follow-up intervals (1, 2, and 5

years) (RELA).[e85] 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% returned to school or work.[e86] While these studies examine 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 (INFER).

Recommendation statement 3

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

*This is the 1 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 < 28 days from injury.

Rationale profile for recommendation 3

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 4	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 5	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 10	Yes
Cost relative to net	Very large 0	Large 1	Moderate 3	Small 8	Yes
Strength of recommenda	R/U	C	B	A	

Recommendation 4

Rationale for recommendation 4

The natural history of DoC is not well-defined, particularly for populations with nontraumatic DoC (EVID), and diagnosis and prognosis can be challenging (EVID). Individuals with DoC can fluctuate between different diagnostic categories such as VS and MCS. Fluctuation is particularly common early in the course of recovery (RELA),[e105] and 1 study suggests a 30% (95% CI 0%–55%) probability of observing behaviors suggestive of MCS in patients diagnosed with VS/UWS when assessments are conducted in the morning (RELA).[e91] Patients with VS may also emerge to MCS over time (EVID). MCS is probably associated with a better prognosis than VS (EVID). Serial examinations, already suggested to improve diagnostic accuracy, may also aid prognosis in view of the relationship between diagnosis and prognosis (INFER).

Recommendation statement 4

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).

Rationale profile for recommendation 4

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 6	Critically 6	Yes
Variation in preferences	Large 0	Moderate 0	Modest 1	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 5

Rationale for recommendation 5

In patients diagnosed with traumatic VS/UWS for at least a month, DRS scores < 26 at 2–3 months post injury, a detectable P300 at 2–3 months post injury, a reactive EEG at 2–3 months post injury, and higher-level activation of the auditory association cortex using BOLD fMRI in response to a familiar voice speaking the patient's name (performed 1–60 months post insult) probably have prognostic utility, suggesting an increased chance of recovering consciousness within 12 months (EVID). In this population, a normal SPECT scan at 1–2 months post injury, lower DRS scores in general 2–3 months post injury, and a detectable P300 2–3 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 6–8 weeks post injury showing corpus callosal lesions, dorsolateral upper brainstem injury, or corona radiata injury are possibly associated with a worse prognosis (remaining in PVS) at 12 months (EVID). In patients diagnosed with nontraumatic VS/UWS, specifically post-anoxic VS/UWS, it is highly probable that CRS-R scores of ≥6 at study entry (more than 1 month after onset) and the presence of SEPs (classified as present when N20 cortical response was recorded on at least 1 side, performed 4.6 ± 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 (EVID). No prognostic models have been developed using these features as a composite to predict long-term outcome (EVID).

Recommendation statement 5 (posttraumatic VS/UWS)

Clinicians should perform the DRS at 2–3 months post injury (Level B) and may assess for the presence of P300 at 2–3 months post injury (Level C based on feasibility) or assess EEG reactivity at 2–3 months post injury (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 imaging 6–8 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 (Level B). Clinicians should perform a SPECT scan 1–2 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 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 speaking the patient's name to assist in prognostication regarding 12-month (post-scan) recovery of consciousness for patients in traumatic VS/UWS 1–60 months post injury (Level C based on feasibility, cost).

Rationale profile for recommendation 5 – part I (DRS assessment)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 8	Critically 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 4	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 2	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Rationale profile for recommendation 5 – part II (P300 assessment)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 2	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or 1	Mildly 1	Very 9	Critically 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 6	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 9	Usually 3	Always 2	Yes
Cost relative to net benefit	Very large 1	Large 3	Moderate 7	Small 3	No
Strength of recommendation	R/U	C	B	A	

Rationale profile for recommendation 5 – part III (EEG reactivity assessment)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 2	Benefit > harm 0	Benefit >> harm 7	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or 0	Mildly 2	Very 9	Critically 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 6	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 6	Usually 4	Always 4	No
Cost relative to net benefit	Very large 0	Large 2	Moderate 8	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Rationale profile for recommendation 5 – part IV (MRI assessment)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 7	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or 1	Mildly 1	Very 10	Critically 2	Yes
Variation in preferences	Large 0	Moderate 0	Modest 8	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 2	Usually 5	Always 7	Yes
Cost relative to net benefit	Very large 1	Large 4	Moderate 7	Small 2	No
Strength of recommendation	R/U	C	B	A	

Rationale profile for recommendation 5 – part V (SPECT assessment)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 1	Benefit >> harm 8	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or 1	Mildly 2	Very 9	Critically 2	No
Variation in preferences	Large 0	Moderate 0	Modest 8	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 5	Usually 9	Always 0	Yes
Cost relative to net benefit	Very large 1	Large 3	Moderate 10	Small 0	Yes
Strength of recommendation	R/U	C	B	A	

Rationale profile for recommendation 5 – part VI (fMRI assessment)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 2	Benefit >> harm 7	Benefit >>> harm 4	No
Importance of outcomes	Not important or 1	Mildly 2	Very 8	Critically 3	No
Variation in preferences	Large 0	Moderate 1	Modest 8	Minimal 5	Yes
Feasible	Rarely 3	Occasionally 10	Usually 1	Always 0	Yes
Cost relative to net benefit	Very large 2	Large 7	Moderate 5	Small 0	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 6

Rationale for recommendation 6

In patients diagnosed with nontraumatic post-anoxic VS/UWS, it is highly probable that CRS-R scores of ≥6 obtained more than 1 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.

Recommendation statement 6 (nontraumatic, post-anoxic VS/UWS)

Clinicians should perform the CRS-R (Level B) and may assess SEPs (Level C based on feasibility) to assist in prognostication regarding recovery of consciousness at 24 months for patients in nontraumatic post-anoxic VS/UWS.

Rationale profile for recommendation 6 – part I (CRS-R assessment)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 6	Critically 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 1	Usually 8	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Rationale profile for recommendation 6 – part II (SEP assessment)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 4	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or 0	Mildly 2	Very 9	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 7	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 7	Usually 3	Always 4	No
Cost relative to net	Very large 1	Large 3	Moderate 5	Small 5	No
Strength of recommenda	R/U	C	B	A	

Recommendation 7

Rationale for recommendation 7

The 1994 AAN Multi-Society Task Force defined VS as "permanent" 3 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 (PRIN).[e2] 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 (RELA).[e27] Relying only on the portion of the Task Force dataset that was extracted from the Traumatic Coma Data Bank[e106] (which appropriately defined VS and reported findings on 25 cases followed after 12 months), 6 patients (14%) recovered consciousness between 1 and 3 years post injury. 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 meeting inclusion criteria evaluated the prognosis of patients with traumatic VS/UWS after 12 months of injury (EVID), 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 2, 3, 4, and 5 years post injury (1 lost to follow-up, 9 died, and 2 remained in VS/UWS), but due to the small sample size, CIs for the possibility of 1 improving were wide (0%, 95% CI 0%–24%) (EVID).[e49]

When considering patients with nontraumatic VS/UWS for at least 1 month, recent studies suggest that some patients 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 (emerge from VS/UWS) at 6 months, and that after 6 months, it is possible that an estimated 7.5% (95% CI 0%–24%) may recover consciousness from nontraumatic VS/UWS (EVID). In 1 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, with the 2 individuals emerging from MCS falling in this later range (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). That is, of 41 patients who remained in VS/UWS at 6 months, 7 additional patients recovered consciousness before 24 months (17%, 95% CI 9%–31%) (EVID).[e62] 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 (PRIN), something accounted for in most but not all publications.

There is additional evidence suggesting that late transition to MCS from VS/UWS is not rare and may occur in as many as 20% of patients who meet the criteria for permanence. 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 (7 traumatic, 3 nontraumatic) recovered consciousness between 14 and 28 months post onset (RELA).[e65] 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 post onset, 8 (47.0%) regained this ability between 1 and 5 years post injury (RELA).[e85]

Although the majority of patients who remain in VS/UWS across the first 3 (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 (RELA).[e107]

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 (INFER). 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. We suggest 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 (EVID). 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 (PRIN).

Recommendation statement 7

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

Rationale profile for recommendation 7

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 4	Critically 8	Yes
Variation in preferences	Large 0	Moderate 2	Modest 4	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 3	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 8

Rationale for recommendation 8

Evidence from the prognosis section of the systematic review 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 (EVID).[e13] 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 (EVID).

As described in the rationale for recommendation 3 above, evidence from the natural history section of the systematic review identified that individuals with a DoC at 1 month post injury may still attain functionally significant recovery after 1 year post injury (EVID), with additional longitudinal studies showing that approximately 20% of patients recover to the level where they could return to work or school.[e85,e86]

Recommendation statement 8

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

Rationale profile for recommendation 8

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 9	Critically 4	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 4	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 9

Rationale for recommendation 9

Patients with DoC lasting at least 28 days may have a prolonged recovery over months to years and many will remain severely disabled (EVID). Employment and personal finances in both the short term and the long term and will be significantly impacted, and these effects will have implications for family members (INFER). Patients and families benefit from planning in advance for an expected prolonged recovery (PRIN).

Recommendation statement 9

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, and applying for disability benefits, and starting estate, caregiver, and long-term care planning (Level A).

Rationale profile for recommendation 9

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 5	Critically 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 10

Rationale for recommendation 10

See rationale for recommendation 7.

Recommendation statement 10

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).

Rationale profile for recommendation 10

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 6	Critically 7	Yes
Variation in preferences	Large 0	Moderate 1	Modest 5	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 11

Rationale for recommendation 11

Pre-expressed wishes of patients with prolonged DoC and values of families of persons with prolonged DoC can be highly variable (PRIN). 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 (PRIN).

Recommendation statement 11

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).

Rationale profile for recommendation 11

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 4	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 11	Yes
Cost relative to net	Very large 0	Large 0	Moderate 4	Small 10	Yes
Strength of recommenda	R/U	C	B	A	

Recommendation 12

Rationale for recommendation 12

Complication rates are high in patients with prolonged DoC and negatively affect morbidity and mortality (RELA).[e78,e89,e108,e109] 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 (INFER). The most common complications observed in patients with prolonged DoC include agitation/aggression, hypertonia, sleep disturbance, and urinary tract infections (RELA).[e107] More severe, complications such as hydrocephalus, pneumonia, and paroxysmal sympathetic hyperactivity can disrupt rehabilitation efforts, as they often require rehospitalization (RELA).[e107] 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 (RELA).[e107]

Recommendation statement 12

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

Rationale profile for recommendation 12

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 2	Critically 11	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 1	Usually 6	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 7	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 13

Rationale for recommendation 13

The potential to experience pain and suffering is an issue frequently raised with respect to treatment, ethical, and legal questions in individuals with DoC (PRIN). 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 (RELA).[e110,e111] Other studies suggest that the relationship between level of consciousness and pain perception is unclear (RELA).[e112,e113] 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 (PRIN) and conflicting evidence regarding the potential of patients in VS or MCS to experience pain and suffering (INFER). Clinicians should be cautious in making definitive conclusions about pain and suffering in individuals with DoC (INFER).

Recommendation statement 13

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).

Rationale profile for recommendation 13 – part I (pain assessment and treatment)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 5	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 7	Critically 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 4	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 6	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Rationale profile for recommendation 13 – part II (counseling on pain)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or 0	Mildly 3	Very 6	Critically 4	No
Variation in preferences	Large 1	Moderate 1	Modest 5	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 1	Usually 2	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 14

Rationale for recommendation 14

Amantadine (100–200 mg twice daily), when administered over a period of4 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 (EVID). Faster recovery reduces the burden of disability, lessens health care costs, and minimizes psychosocial stressors in patients and caregivers (PRIN).

Recommendation statement 14

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

Rationale profile for recommendation 14

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 7	Critically 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 8	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 3	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 15

Rationale for recommendation 15

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 (EVID) and many have associated risks (PRIN). Families may pursue these treatments even in the absence of evidence because they are often desperate for ways to help their loved one (PRIN), and because interventions supported by high-quality evidence are sparse (EVID). 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 (PRIN).

Recommendation statement 15

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

Rationale profile for recommendation 15 – part I (counseling on treatment risk and harms)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or 0	Mildly 2	Very 7	Critically 4	Yes
Variation in preferences	Large 1	Moderate 4	Modest 5	Minimal 3	No
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Rationale profile for recommendation 15 – part II (counseling on nonvalidated treatments)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 8	Critically 4	Yes
Variation in preferences	Large 1	Moderate 2	Modest 7	Minimal 3	No
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Rationale profile for recommendation 15 – part III (counseling on natural recovery vs treatment effects)

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 2	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or 0	Mildly 3	Very 6	Critically 4	No
Variation in preferences	Large 1	Moderate 1	Modest 7	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 2	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Recommendations concerning the pediatric population

Recommendation 16

Rationale for recommendation 16

Using the same screening criteria applied to adults with prolonged DoC, no evidence was identified regarding the diagnosis of children with prolonged DoC (EVID). 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 (INFER).

Recommendation statement 16

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).

Rationale profile for recommendation 16

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 6	Critically 6	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 17

Rationale for recommendation 17

The natural history of DoC in children is not well defined (EVID). 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 (EVID). No other evidence regarding prognosis in pediatric DoC populations was identified (EVID).

Recommendation statement 17

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).

Rationale profile for recommendation 17

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 6	Critically 6	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 18

Rationale for recommendation 18

No therapeutic studies identified for this systematic review enrolled pediatric populations, and the only therapeutic intervention shown to have efficacy in adults (aged 16–65 years) with DoC is amantadine (EVID). 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 (RELA).

Recommendation statement 18

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

Rationale profile for recommendation 18

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or 0	Mildly 3	Very 5	Critically 4	No
Variation in preferences	Large 0	Moderate 2	Modest 3	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 11	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

E-REFERENCES

e1. Plum F. and J.B. Posner. The Diagnosis of Stupor and Coma, 3rd ed. Philadelphia: F.A. Davis Co., 1982.
e2. Ashwal S, Cranford R, Bernat JL, et al. Medical aspects of the persistent vegetative state: (First of two parts). N Engl J Med 1994;330:1499-1508.
e3. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. Neurology 2002;58:349-353.
e4. Sazbon L, Groswasser Z. Medical complications and mortality of patients in the postcomatose unawareness (PC-U) state. Acta Neurochirurgica 1991;112:110-112.
e5. Laureys S, Celesia GG, Cohadon F, et al.; for the European Task Force on Disorders of Consciousness Unresponsive wakefulness syndrome: A new name for the vegetative state or apallic syndrome. BMC Med 2010;8:68.
e6. Jennett B. The vegetative state. J Neurol Neurosurg Psychiatry 2002;73:355-357.
e7. Cranford RE. The persistent vegetative state: the medical reality (getting the facts straight). Hastings Cent Rep 1988;18:27-32.
e8. Spudis EV. The persistent vegetative state--1990. J Neurol Sci 1991;102:128-136.
e9. Tresch DD, Sims FH, Duthie EH, Goldstein MD, Lane PS. Clinical characteristics of patients in the persistent vegetative state. Arch Intern Med 1991;151:930-932.
e10. Strauss DJ, Ashwal S, Day SM, Shavelle RM. Life expectancy of children in vegetative and minimally conscious states. Pediatr Neurol 2000;23:312-319.
e11. Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J Neurol 2011;258:1373-1384.
e12. Giacino JT SN. The Minimally Conscious State: Clinical Features, Pathophysiology and Therapeutic Implications. In: Laureys SL TG, ed. The Neurology of Consciousness: Cognitive Neuroscience and Neuropathology. Philadelphia: Elsevier, 2009.
e13. Giacino JT, Kalmar K. The vegetative and minimally conscious states: a comparison of clinical features and functional outcome. J Head Trauma Rehabil 1997;12:36-51.
e14. Lammi MH, Smith VH, Tate RL, Taylor CM. The minimally conscious state and recovery potential: a follow-up study 2 to 5 years after traumatic brain injury. Arch Phys Med Rehabil 2005;86:746-754.
e15. Eilander HJ, Wijnen VJ, Scheirs JG, de Kort PL, Prevo AJ. Children and young adults in a prolonged unconscious state due to severe brain injury: outcome after an early intensive neurorehabilitation programme. Brain Inj 2005;19:425-436.
e16. National Institutes of Health. Consensus conference. Rehabilitation of persons with traumatic brain injury. Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury. JAMA 1999;282:974-983.
e17. Practice parameters: assessment and management of patients in the persistent vegetative state (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1995;45:1015-1018.
e18. Schnakers C, Vanhaudenhuyse A, Giacino J, et al. Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. BMC Neurol 2009;9:35.

e19. Childs NL, Mercer WN, Childs HW. Accuracy of diagnosis of persistent vegetative state. Neurology 1993;43:1465-1467.
e20. Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. BMJ 1996;313:13-16.
e21. Nakase-Richardson R, Yablon SA, Sherer M, Evans CC, Nick TG. Serial yes/no reliability after traumatic brain injury: Implications regarding the operational criteria for emergence from the minimally conscious state. J Neurol Neurosurg Psychiatry 2008;79:216-218.
e22. Seel RT, Sherer M, Whyte J, et al. Assessment scales for disorders of consciousness: evidence-based recommendations for clinical practice and research. Arch Phys Med Rehabil 2010;91:1795-1813.
e23. Rodriguez Moreno D, Schiff ND, Giacino J, Kalmar K, Hirsch J. A network approach to assessing cognition in disorders of consciousness. Neurology 2010;75:1871-1878.
e24. Coleman MR, Davis MH, Rodd JM, et al. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. Brain 2009;132:2541-2552.
e25. Schiff ND, Rodriguez-Moreno D, Kamal A, et al. fMRI reveals large-scale network activation in minimally conscious patients. Neurology 2005;64:514-523.
e26. Laureys S, Faymonville ME, Degueldre C, et al. Auditory processing in the vegetative state. Brain 2000;123:1589-1601.
e27. Childs NL, Mercer WN. Brief report: Late improvement in consciousness after post-traumatic vegetative state. N Engl J Med 1996;334:24-25.
e28. Giacino J. Revisiting the vegetative state: Major developments over the last decade. In: McDeavitt J, ed. State of the Art Reviews in Physical Medicine and Rehabilitation: Traumatic Brain Injury. Philadelphia: Hanley and Belfus, Inc., 2001: 399-415.
e29. American Academy of Neurology. Clinical Practice Guideline Process Manual, 2011 ed. Available at: https://www.aan.com/policy-and-guidelines/guidelines/about-guidelines2/. Accessed September 2, 2016.
e30. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-926.
e31. Habbal D, Gosseries O, Noirhomme Q, et al. Volitional electromyographic responses in disorders of consciousness. Brain Inj 2014;28:1171-1179.
e32. Charland-Verville V, Lesenfants D, Sela L, et al. Detection of response to command using voluntary control of breathing in disorders of consciousness. Front Hum Neurosci 2014;8:1020.
e33. Forgacs PB, Conte MM, Fridman EA, Voss HU, Victor JD, Schiff ND. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. Ann Neurol 2014;76:869-879.
e34. Casarotto S, Comanducci A, Rosanova M, et al. Stratification of unresponsive patients by an independently validated index of brain complexity. Ann Neurol 2016;80:718-729.
e35. Estraneo A, Loreto V, Guarino I, et al. Standard EEG in diagnostic process of prolonged disorders of consciousness. Clin Neurophysiol 2016;127:2379-2385.
e36. Monti MM, Rosenberg M, Finoia P, Kamau E, Pickard JD, Owen AM. Thalamo-frontal connectivity mediates top-down cognitive functions in disorders of consciousness. Neurology 2015;84:167-173.
e37. Lesenfants D, Habbal D, Chatelle C, Schnakers C, Laureys S, Noirhomme Q. Electromyographic decoding of response to command in disorders of consciousness. Neurology 2016;87:2099-2107.

e38. Naro A, Russo M, Leo A, et al. Cortical responsiveness to nociceptive stimuli in patients with chronic disorders of consciousness: do C-fiber laser evoked potentials have a role? PLoS One 2015;10:e0144713. eCollection 2015.
e39. Chennu S, Finoia P, Kamau E, et al. Dissociable endogenous and exogenous attention in disorders of consciousness. Neuroimage Clin 2013;3:450-461.
e40. Kotchoubey B, Yu T, Mueller F, Vogel D, Veser S, Lang S. True or false? Activations of language-related areas in patients with disorders of consciousness. Curr Pharm Des 2014;20:4239-4247.
e41. Rosazza C, Andronache A, Sattin D, et al. Multimodal study of default-mode network integrity in disorders of consciousness. Ann Neurol [Epub March 11, 2016].
e42. Gosseries O, Schnakers C, Ledoux D, et al. Automated EEG entropy measurements in coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state. Funct Neurol 2011;26:25-30.
e43. Holler Y, Bergmann J, Kronbichler M, et al. Preserved oscillatory response but lack of mismatch negativity in patients with disorders of consciousness. Clin Neurophysiol 2011;122:1744-1754.
e44. Stender J, Gosseries O, Bruno MA, et al. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. Lancet 2014;384:514-522.
e45. Zheng ZS, Reggente N, Lutkenhoff E, Owen AM, Monti MM. Disentangling disorders of consciousness: Insights from diffusion tensor imaging and machine learning. Hum Brain Mapp 2017;38:431-443.
e46. Sazbon L, Zagreba F, Ronen J, Solzi P, Costeff H. Course and outcome of patients in vegetative state of nontraumatic aetiology. J Neurol Neurosurg Psychiatry 1993;56:407-409.
e47. Cavinato M, Freo U, Ori C, et al. Post-acute P300 predicts recovery of consciousness from traumatic vegetative state. Brain Inj 2009;23:973-980.
e48. Sara M, Pistoia F, Pasqualetti P, Sebastiano F, Onorati P, Rossini PM. Functional isolation within the cerebral cortex in the vegetative state: A nonlinear method to predict clinical outcomes. Neurorehabil Neural Repair 2011;25:35-42.
e49. Luaute J, Maucort-Boulch D, Tell L, et al. Long-term outcomes of chronic minimally conscious and vegetative states. Neurology 2010;75:246-252.
e50. Skandsen T, Lund TI, Fredriksli O, Vik A. Global outcome, productivity and epilepsy 3-8 years after severe head injury. The impact of injury severity. Clin Rehabil 2008;22:653-662.
e51. Noe E, Olaya J, Navarro MD, et al. Behavioral recovery in disorders of consciousness: a prospective study with the Spanish version of the Coma Recovery Scale-Revised. Arch Phys Med Rehabil 2012;93:428-433.
e52. Danze F, Veys B, Lebrun T, et al. Prognostic factors of post-traumatic vegetative states: 522 cases. Neurochirurgie 1994;40:348-357; discussion 357-348.
e53. Sazbon L, Groswasser Z. Outcome in 134 patients with prolonged posttraumatic unawareness. Part 1: Parameters determining late recovery of consciousness. J Neurosurg 1990;72:75-80.
e54. Pascarella A, Trojano L, Loreto V, Bilo L, Moretta P, Estraneo A. Long-term outcome of patients with disorders of consciousness with and without epileptiform activity and seizures: a prospective single centre cohort study. J Neurol 2016;263:2048-2056.

e55. Bagnato S, Boccagni C, Sant'Angelo A, Fingelkurts AA, Fingelkurts AA, Galardi G. Longitudinal assessment of clinical signs of recovery in patients with unresponsive wakefulness syndrome after traumatic or nontraumatic brain injury. J Neurotrauma 2017;34:535-539.
e56. Mateen FJ, Niu JW, Gao S, et al. Causes and outcomes of persistent vegetative state in a Chinese versus American referral hospital. Neurocrit Care 2013;18:266-270.
e57. Tsubokawa T, Yamamoto T, Katayama Y. Prediction of outcome of prolonged coma caused by brain damage. Brain Inj 1990;4:329-337.
e58. Pape TL, Heinemann AW, Kelly JP, Hurder AG, Lundgren S. A measure of neurobehavioral functioning after coma. Part I: Theory, reliability, and validity of Disorders of Consciousness Scale. J Rehabil Res Dev 2005;42:1-17.
e59. Dolce G, Lucca LF, Candelieri A, Rogano S, Pignolo L, Sannita WG. Visual pursuit in the severe disorder of consciousness. J Neurotrauma 2011;28:1149-1154.
e60. Wilson SL, Gill-Thwaites H. Early indication of emergence from vegetative state derived from assessments with the SMART--a preliminary report. Brain Inj 2000;14:319-331.
e61. Beis JM, Seyer JL, Brugerolle B, et al. Care protocol for persistent vegetative states (PVS) and minimally conscious state (MSC) in Lorraine: retrospective study over an 18-year period. Ann Phys Rehabil Med 2009;52:374-381.
e62. Estraneo A, Moretta P, Loreto V, et al. Predictors of recovery of responsiveness in prolonged anoxic vegetative state. Neurology 2013;80:464-470.
e63. Bagnato S, Minafra L, Bravata V, et al. Brain-derived neurotrophic factor (Val66Met) polymorphism does not influence recovery from a post-traumatic vegetative state: a blinded retrospective multi-centric study. J Neurotrauma 2012;29:2050-2059.
e64. Giacino JT. Disorders of consciousness: differential diagnosis and neuropathologic features. Semin Neurol 1997;17:105-111.
e65. Estraneo A, Moretta P, Loreto V, Lanzillo B, Santoro L, Trojano L. Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. Neurology 2010;75:239-245.
e66. Pape TL, Tang C, Guernon A, et al. Predictive value of the Disorders of Consciousness Scale (DOCS). PMR 2009;1:152-161.
e67. Kotchoubey B, Lang S, Mezger G, et al. Information processing in severe disorders of consciousness: Vegetative state and minimally conscious state. Clin Neurophysiol 2005;116:2441-2453.
e68. Groswasser Z, Sazbon L. Outcome in 134 patients with prolonged posttraumatic unawareness. Part 2: Functional outcome of 72 patients recovering consciousness. J Neurosurg 1990;72:81-84.
e69. Nayak P, Mahapatra A. Single photon emission computed tomography scanning: A predictor of outcome in vegetative state of head injury. J Neurosci Rural Pract 2011;2:12-16.
e70. Goodwin L. Use of MRI in prediction of recovery from persistent vegetative state. J Insur Med 1998;30:113-114.
e71. Wang F, Di H, Hu X, et al. Cerebral response to subject's own name showed high prognostic value in traumatic vegetative state. BMC Med 2015;13:83.
e72. Sazbon L, Fuchs C, Costeff H. Prognosis for recovery from prolonged post-traumatic unawareness: Logistic analysis. J Neurol Neurosurg and Psychiatry 1991;54:149-152.
e73. Whyte J, Katz D, Long D, et al. Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: A multicenter study. Arch Phys Med Rehabil 2005;86:453-462.

e74. Zheng X, Chen M, Li J, Cao F. Prognosis in prolonged coma patients with diffuse axonal injury assessed by somatosensory evoked potentia. Neural Regen Res 2013;8:948-954.
e75. Kriel RL, Krach LE, Jones-Saete C. Outcome of children with prolonged unconsciousness and vegetative states. Pediatr Neurol 1993;9:362-368.
e76. Heindl UT, Laub MC. Outcome of persistent vegetative state following hypoxic or traumatic brain injury in children and adolescents. Neuropediatrics 1996;27:94-100.
e77. Vogel D, Markl A, Yu T, Kotchoubey B, Lang S, Muller F. Can mental imagery functional magnetic resonance imaging predict recovery in patients with disorders of consciousness? Arch Phys Med Rehabil 2013;94:1891-1898.
e78. Ganesh S, Guernon A, Chalcraft L, Harton B, Smith B, Louise-Bender Pape T. Medical comorbidities in disorders of consciousness patients and their association with functional outcomes. Arch Phys Med Rehabil 2013;94:1899-1907.
e79. Arnaldi D, Terzaghi M, Cremascoli R, et al. The prognostic value of sleep patterns in disorders of consciousness in the sub-acute phase. Clin Neurophysiol 2016;127:1445-1451.
e80. Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med 2012;366:819-826.
e81. Krewer C, Luther M, Koenig E, Muller F. Tilt table therapies for patients with severe disorders of consciousness: a randomized, controlled trial. PLoS One 2015;10:e0143180.
e82. Herrold AA, Pape TL, Guernon A, Mallinson T, Collins E, Jordan N. Prescribing multiple neurostimulants during rehabilitation for severe brain injury. ScientificWorldJournal 2014;2014:964578.
e83. Yamamoto T, Katayama Y, Kobayashi K, Oshima H, Fukaya C, Tsubokawa T. Deep brain stimulation for the treatment of vegetative state. Eur J Neurosci 2010;32:1145-1151.
e84. Yamamoto T, Katayama Y, Obuchi T, Kobayashi K, Oshima H, Fukaya C. Deep brain stimulation and spinal cord stimulation for vegetative state and minimally conscious state. World Neurosurg 2013;80:S30.e31-e39.
e85. Nakase-Richardson R, Whyte J, Giacino JT, et al. Longitudinal outcome of patients with disordered consciousness in the NIDRR TBI Model Systems Programs. J Neurotrauma 2012;29:59-65.
e86. Katz DI, Polyak M, Coughlan D, Nichols M, Roche A. Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1-4 year follow-up. Prog Brain Res 2009;177:73-88.
e87. Lovstad M, Froslie KF, Giacino JT, Skandsen T, Anke A, Schanke AK. Reliability and diagnostic characteristics of the JFK coma recovery scale-revised: exploring the influence of rater's level of experience. J Head Trauma Rehabil 2010;25:349-356.
e88. Turgeon AF, Lauzier F, Simard JF, et al.; for the Canadian Critical Care Trials Group. Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. CMAJ 2011;183:1581-1588.
e89. Whyte J, Nordenbo AM, Kalmar K, et al. Medical complications during inpatient rehabilitation among patients with traumatic disorders of consciousness. Arch Phys Med Rehabil 2013;94:1877-1883.
e90. Davidson GH, Hamlat CA, Rivara FP, Koepsell TD, Jurkovich GJ, Arbabi S. Long-term survival of adult trauma patients. JAMA 2011;305:1001-1007.
e91. Cortese MD, Riganello F, Arcuri F, et al. Coma recovery scale-r: variability in the disorder of consciousness. BMC Neurol 2015;15:186.

e92. Candelieri A, Cortese MD, Dolce G, Riganello F, Sannita WG. Visual pursuit: within-day variability in the severe disorder of consciousness. J Neurotrauma 2011;28:2013-2017.
e93. Bardin JC, Fins JJ, Katz DI, et al. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. Brain 2011;134:769-782.
e94. Schnakers C, Zasler N. Assessment and management of pain in patients with disorders of consciousness. PM&R 2015;7:S270-S277.
e95. Majerus S, Gill-Thwaites H, Andrews K, Laureys S. Behavioral evaluation of consciousness in severe brain damage. Prog Brain Res 2005;150:397-413.
e96. Smart CM, Giacino JT, Cullen T, et al. A case of locked-in syndrome complicated by central deafness. Nat Clin Pract Neurol 2008;4:448-453.
e97. Laureys S, Pellas F, Van Eeckhout P, et al. The locked-in syndrome: what is it like to be conscious but paralyzed and voiceless? Prog Brain Res 2005;150:495-511.
e98. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004;85:2020-2029.
e99. Whyte J, DiPasquale MC, Vaccaro M. Assessment of command-following in minimally conscious brain injured patients. Arch Phys Med Rehabil 1999;80:653-660.
e100. Shiel A, Horn SA, Wilson BA, Watson MJ, Campbell MJ, McLellan DL. The Wessex Head Injury Matrix (WHIM) main scale: a preliminary report on a scale to assess and monitor patient recovery after severe head injury. Clin Rehabil 2000;14:408-416.
e101. Gill-Thwaites H, Munday R. The Sensory Modality Assessment Rehabilitation Technique (SMART): a valid and reliable assessment for the vegetative and minimally conscious state patient. Brain Inj 2004;18:1255-1269.
e102. Ansell BJ, Keenan JE. The Western Neuro Sensory Stimulation Profile: a tool for assessing slow-to-recover head-injured patients. Arch Phys Med Rehabil 1989;70:104-108.
e103. Rader MA, Ellis DW. The Sensory Stimulation Assessment Measure (SSAM): a tool for early evaluation of severely brain-injured patients. Brain Inj 1994;8:309-321.
e104. Sitt JD, King JR, El Karoui I, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain 2014;137:2258-2270.
e105. Riganello F, Cortese MD, Dolce G, Lucca LF, Sannita WG. The autonomic system functional state predicts responsiveness in disorder of consciousness. J Neurotrauma 2015;32:1071-1077.
e106. Marshall LF, Becker DP, Bowers SA, et al. The National Traumatic Coma Data Bank. Part 1: Design, purpose, goals, and results. J Neurosurg 1983;59:276-284.
e107. Whyte J, Nakase-Richardson R. Disorders of consciousness: outcomes, comorbidities, and care needs. Arch Phys Med Rehabil 2013;94:1851-1854.
e108. Nakase-Richardson R, McNamee S, Howe LL, et al. Descriptive characteristics and rehabilitation outcomes in active duty military personnel and veterans with disorders of consciousness with combat- and noncombat-related brain injury. Arch Phys Med Rehabil 2013;94:1861-1869.
e109. Nakase-Richardson R, Tran J, Cifu D, et al. Do rehospitalization rates differ among injury severity levels in the NIDRR Traumatic Brain Injury Model Systems program? Arch Phys Med Rehabil 2013;94:1884-1890.

e110. Boly M, Faymonville M-E, Peigneux P, et al. Cerebral processing of auditory and noxious stimuli in severely brain injured patients: Differences between VS and MCS. Neuropsychol Rehabil 2005;15:283-289.
e111. Boly M, Faymonville M-E, Schnakers C, et al. Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol 2008;7:1013-1020.
e112. Chatelle C, Thibaut A, Whyte J, De Val MD, Laureys S, Schnakers C. Pain issues in disorders of consciousness. Brain Inj 2014;28:1202-1208.
e113. Yu T, Lang S, Vogel D, Markl A, Muller F, Kotchoubey B. Patients with unresponsive wakefulness syndrome respond to the pain cries of other people. Neurology 2013;80:345-352.
e114. Doiron MJ CA, Hunsaker E, Beninato M, Giacino J. Disability Rating Scale Criteria as a Screen for Consciousness. Arch Phys Med Rehabil 2014;95:e57-e58.
e115. Katz D, Whyte J, Chang H, et al. Effect of lesion burden on recovery and on response to amantadine in patients with disorders of consciousness after traumatic brain injury. Brain Inj 2016;30:481-817.
e116. Du B, Shan A, Zhang Y, Zhong X, Chen D, Cai K. Zolpidem arouses patients in vegetative state after brain injury: quantitative evaluation and indications. Am J Med Sci 2014;347:178-182.
e117. Whyte J, Rajan R, Rosenbaum A, et al. Zolpidem and restoration of consciousness. Am J Phys Med Rehabil 2014;93:101-113.
e118. Doman G, Wilkinson R, Dimancescu MD, Pelligra R. The effect of intense multi-sensory stimulation on coma arousal and recovery. Neuropsychological Rehab 2007;3:203-212.
e119. Seledtsov VI, Rabinovich SS, Parlyuk OV, et al. Cell transplantation therapy in reanimating severely head-injured patients. Biomed Pharmacother 2005;59:415-420.
e120. Kondratiev AN, Nazarov RV, Kondratieva EA. The studies of autologous stem cells in patients with a prolonged unconscious state after traumatic brain injury. Eur J Anaesthesiol 2012;29:S20.
e121. Aquilani R, Boselli M, Boschi F, et al. Branched-chain amino acids may improve recovery from a vegetative or minimally conscious state in patients with traumatic brain injury: a pilot study. Arch Phys Med Rehabil 2008;89:1642-1647.
e122. Sahni T, Jain M, Prasad R, Sogani SK, Singh VP. Use of hyperbaric oxygen in traumatic brain injury: retrospective analysis of data of 20 patients treated at a tertiary care centre. Br J Neurosurg 2012;26:202-207.
e123. Schnakers C. Do sensory stimulation programs have an impact on consciousness recovery? Arch Phys Med Rehabil 2014;95:e52.