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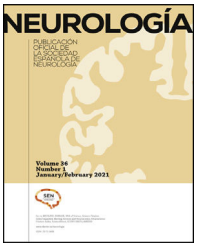

REVIEW ARTICLE

Guideline: Neurorehabilitation in patients with disorder of consciousness. Recommendations from the Spanish Society of Neurorehabilitation

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Abstract
Introduction: Clinical practice guidelines in neurorehabilitation for adults with disorders of consciousness by the Spanish Neurorehabilitation Society. This document is based on a review of international clinical practice guidelines published between 2015 and 2022.
Method: A total of 7 articles, corresponding to 5 clinical practice guidelines published between 2015 and 2022, were selected by the group of authors from a pool of 48 bibliographic references extracted from various databases in accordance with predefined search criteria. Following this review, forty recommendations were formulated and subjected to evaluation by an expert committee using a 9-point Likert scale: 1—3 (inappropriate recommendation), 4—6 (uncertain

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Unresponsive wakefulness syndrome;
Practice guideline

recommendation), and 7—9 (appropriate recommendation), following the methodology of the ''Modified Nominal Group Technique.'' Any recommendation endorsed by at least 75% of the experts as ''appropriate'' (with a score of 7—9) was considered accepted.
Conclusions: This document presents 40 recommendations categorised according to the level of evidence provided by the reviewed studies. These recommendations represent a consensus among experts and pertain to various aspects related to: 1) clinical assessment, 2) complementary diagnostic tests, 3) prognosis, and 4) treatment in this specific population.

PALABRAS CLAVE
Neurorrehabilitación;
Daño cerebral adquirido;
Estados alterados de la consciencia;
Estado de mínima consciencia;
Estado vegetativo;
Estado de vigilia sin respuesta;
Guía clínica

Guía: Neurorrehabilitación en pacientes en estados alterados de la consciencia. Recomendaciones de la Sociedad Española de Neurorrehabilitación

Resumen
Introducción: Guía para la práctica clínica en neurorrehabilitación de personas adultas en estado alterado de la consciencia (EAC) de la Sociedad Española de Neurorrehabilitación. Documento basado en la revisión de guías de práctica clínica internacionales publicadas entre 2015—2022.
Método: Un total de 7 artículos correspondientes a 5 guías de práctica clínica publicadas entre 2015—2022, fueron seleccionadas por el grupo de autores de un total de 48 referencias bibliográficas extraídas de diferentes bases de datos de acuerdo a los criterios de búsqueda. En base a dicha revisión se establecieron cuarenta recomendaciones sometidas a evaluación por un comité de expertos que evaluaron cada recomendación con una escala de 9 puntos de tipo Likert: 1—3 (recomendación inapropiada), 4—6 (recomendación incierta) y 7—9 (recomendación apropiada), de acuerdo a la metodología del *Modified Nominal Group Technique*. Toda recomendación, valorada por al menos un 75% de los expertos como «apropiada» (puntuación: 7—9) se consideró como aceptada.
Conclusiones: Se establecen 40 recomendaciones según el nivel de evidencia que ofrecen los estudios revisados referentes a aspectos consensuados entre expertos dirigidos a definir aspectos relacionados con la: 1) evaluación clínica, 2) pruebas complementarias, 3) pronóstico y 4) tratamiento, en esta población.

Introduction

Disorders of consciousness (DoC) constitute a clinical challenge in terms of diagnosis, prognosis, and treatment.[1—5] This study, in line with previous works by the Spanish Society of Neurorehabilitation (SENR, for its Spanish initials), is intended to offer guidance for clinical practice in the neurorehabilitation of patients with DoC, in accordance with the best and most recent evidence currently available. On behalf of the SENR, we aim to provide the clinicians responsible for these patients with objective information to support decision-making and to share practical information ensuring the best quality care in terms of efficacy, expectation management, and the planning of care resources and needs according to the individual clinical profile of this patient population. This is particularly important given that the prognosis of many of these patients involves high levels of dependency. To that end, we reviewed and extracted data and levels of evidence to establish a consensus position on 4 key aspects of the neurorehabilitation of patients with DoC, from clinical practice guidelines (CPG) and other consensus statements published by different national and international organisations between 2015 and 2022.

Methods

In January 2021, the Executive Board of the SENR established a multidisciplinary working group comprising 5 SENR members (2 neuropsychologists, 2 biomedical engineers, and a general physician), to be directed by 2 coordinators (a neurologist and a neuropsychologist) with over 20 years' clinical and research experience in the field of neurorehabilitation, who were responsible for selecting content and searching the literature for information sources to draft the document. During 2021 and 2022, the working group held in-person and online meetings to establish the framework of action of the guidelines and the different content proposed.

The contents of these guidelines are grouped into 4 areas or dimensions that were established to be clinically relevant according to consensus by the working group:

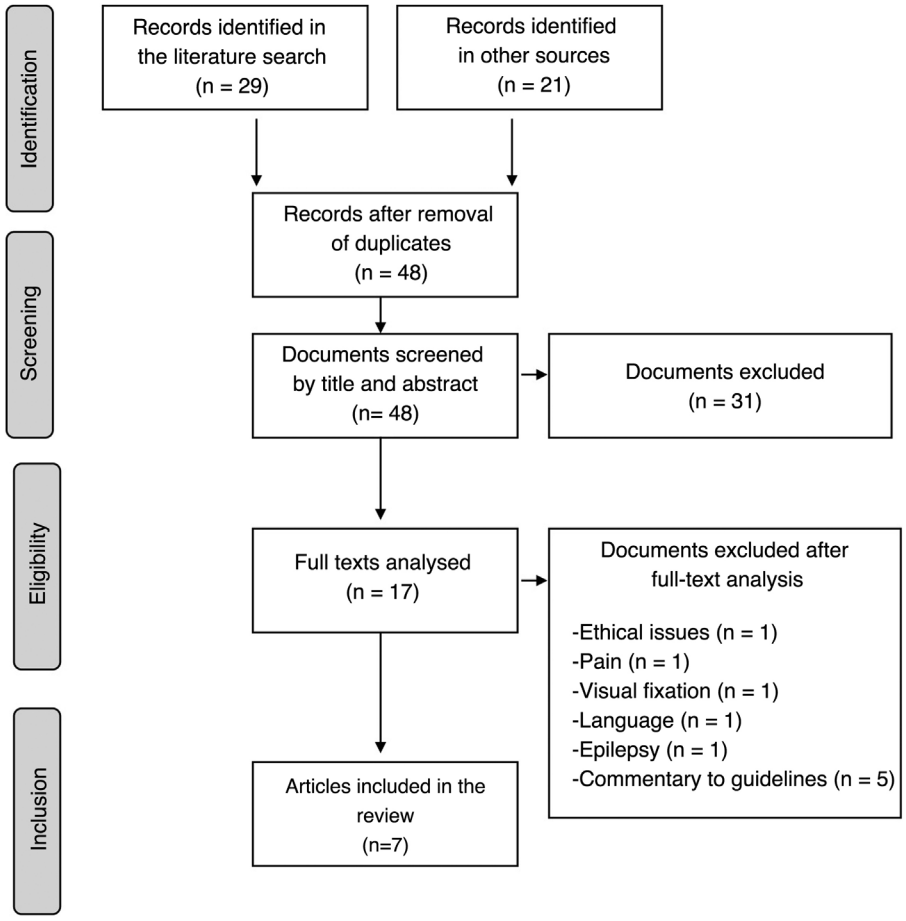

Figure 1 Flow diagram summarising the study selection process.

- Clinical assessment. What clinical considerations are important in the evaluation of these patients?
- Complementary testing. What complementary examinations should be performed in the assessment of these patients?
- Prognosis. What is the prognosis in terms of mortality, recovery of consciousness, and functional status? What predictive variables have been identified for each of these aspects?
- Treatment. What are the main therapeutic interventions currently used in these patients, and what is their level of evidence?

These guidelines were developed according to the methodology established by the SENR for the drafting of consensus statements. The 2 coordinators identified eligible articles in a literature search of PubMed and other databases (MEDLINE [Ovid], CINAHL [EBSCO], Web of Science, PEDro, Cochrane Central Register of Controlled Trials, and Cochrane Stroke Group Trials Register), and on the websites of professional societies of rehabilitation medicine and repositories of CPGs. Potentially relevant studies published between December 2015 and December 2022 were retrieved and their relevance evaluated according to the criteria mentioned above. The literature search yielded a total of 48 articles, after excluding duplicate studies. Of these, 31 were removed after reading the titles and abstracts. The 17 remaining articles were read in full text and screened according to the inclusion criteria established (Fig. 1). At the end of this process, 7 articles were finally included in the study, corresponding to 5 CPGs (Table 1).[6–12] The selected CPGs were assigned to the 5 members of the working group, who extracted the level of evidence and the grade or strength of recommendation with respect to each of the questions mentioned above. The information extracted in this process was reviewed by the 2 coordinators and summarised in a table of recommendations, which was used by the working group to agree a set of recommendations for each of the questions considered, based on the best possible level of evidence (Table 2).

Based on these initial recommendations, the definitive version was established using a formal consensus methodology, the modified nominal group technique.[13] The consensus process comprised 2 phases. The review team comprised 13 experts (6 physicians specialising in physical and rehabilitation medicine, 3 neuropsychologists, 2 neurologists, one psychiatrist, and one physiotherapist) who have sat on the Executive Board of the SENR in the last 10 years. In the first phase, all experts were sent an e-mail with a summary of the available evidence on each of the main clinical areas, as well as a link to the proposed guidelines drafted by the authors, with an evaluation instrument. Reviewers were asked to rate each of the recommendations on a 9-point Likert-type scale, as follows: 1—3 points (unsuitable recommendation); 4—6 points (uncertain recommendation); 7—9 points (suitable recommendation). In

Table 1 Guidelines included in the study.

Authors	Country	Contents	Date	Language
EAN[14]	Europe	ABI	2020	English
ACRM and NIDILRR (TBIMS)[7]	USA	ABI	2020	English
RCP[11]	United Kingdom	ABI	2020	English
AAN, ACRM, and NIDILRR[15—17]	USA	ABI	2018	English
INESS-ONF[12]	Canada	TBI	2018	English

Authors: author, society, or authority that published the guidelines (reference). Country: country or region where the guidelines were published. Contents: patient population addressed in the recommendations. Date: year of publication of the latest update of the document.
AAN: American Academy of Neurology; ABI: acquired brain injury; ACRM: American Congress of Rehabilitation Medicine; EAN: European Academy of Neurology; INESS-ONF: Institute National d'Éxcellence en Santé et en Services Sociaux - Ontario Neurotrauma Foundation; NIDILRR (TBIMS): National Institute on Disability, Independent Living and Rehabilitation Research (Traumatic Brain Injury Model Systems); RCP: Royal College of Physicians; TBI: traumatic brain injury.

Table 2 Levels of evidence and grades of recommendation.

Level of evidence	CEBM	GRADE	Grade of recommendation in this study
1a, 1b	A	Strong, with moderate or high level of evidence	High
2a, 2b	B	Strong, with low level of evidence Weak, with high level of evidence	Moderate
3a, 3b, 4, 5	C	Weak, with moderate or low level of evidence	Low

Adapted from Centre for Evidence-Based Medicine (CEBM) and Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

this phase, participants undertook a first round of individual voting on the recommendations. All recommendations considered appropriate (7—9 points) by at least 75% of reviewers were considered to have been accepted, and were therefore subject only to minor changes. If necessary, any recommendations with less than 75% agreement could be reformulated and undergo a second round of voting in the second phase. Finally, those recommendations that were not accepted in this final stage were not included in the consensus guidelines.

Summary of recommendations

A total of 40 recommendations were drafted. All recommendations were approved by over 75% of experts in the first round of voting; therefore, a second round of voting was not needed. Two recommendations were considered suitable by 90% of experts, with 100% agreement for all of the remaining recommendations; mean scores ranged from 8.3 to 9 points. The percentage of agreement and mean score (range, 1—9) are shown for each of the final recommendations.

Clinical assessment. What clinical considerations are important in the evaluation of these patients?

Table 3 presents the main recommendations extracted from the selected CPGs regarding the clinical assessment of these patients, according to the level of evidence.

Recommendation 1 (level of agreement: 100%, score: 8.7/9)

The diagnosis of patients with DoC is fundamentally clinical, and based on observation (preferably using standardised, validated clinical scales) of the patient's behaviours, actions, and other acts, whether spontaneous or targeted, in response to increasingly complex stimuli in their surroundings.

Who these patients should be assessed by

Recommendation 2 (level of agreement: 90%, score: 8.5/9)

Assessment of patients with DoC must be performed by a transdisciplinary team of professionals with specialist training in the management of patients with high levels of clinical and neurological complexity.

How these patients should be assessed

Recommendation 3 (level of agreement: 100%, score: 9/9)

Patients must be assessed systematically; wherever possible, assessment should employ clinical scales or other standardised tools validated in this population, according to the clinical criteria described in the existing evidence-based guidelines.

Recommendation 4 (level of agreement: 100%, score: 8.9/9)

The Coma Recovery Scale-Revised (CRS-R) is recommended, as well as such other scales as the Full Outline of Unresponsiveness (FOUR) scale (in the acute phase); both the total score and section subscores should be taken into account.

Recommendation 5 (level of agreement: 100%, score: 8.6/9)

As it is usually visual responses that mark the clinical change from vegetative state (VS)/unresponsive wakefulness syndrome (UWS) to minimally conscious state (MCS),

Table 3 Evaluation of patients with disorders of consciousness. Summary of recommendations from the guidelines reviewed, according to level/grade of evidence.

The CRS-R is the scale of choice for the diagnostic classification of level of consciousness in these patients.	High level
• This scale may be used both in subacute situations (patients in ICU with the minimal possible level of sedation) and in chronic cases requiring long-term care. • Given the time required to administer the CRS-R (15—60 minutes) and the need for qualified, experienced professionals, other briefer methods may be used for regular follow-up, always taking into account the fact that any other method will have lower sensitivity for detecting patients in MCS. • Data must be recorded from each subsection, or the modified total score should be used, as the total score may not distinguish between UWS and MCS. • Given their capacity to affect the results, the following potential confounding factors should be taken into account: motor, visual, auditory, and/or cognitive deficits (attention, memory, language, mental flexibility, etc); intubation; sedation; and certain environmental variables: the presence/absence of family members may increase visual responses, for instance.	Strong, with moderate level of evidence (EAN: European guidelines)
The GCS should be replaced with the FOUR scale in the assessment of level of consciousness in these patients in the acute phase or during their stay at the ICU. Although the FOUR scale is less sensitive than the CRS-R, its use is appropriate in settings where the time available for assessment is usually limited and patients may be intubated. Unlike the GCS, the FOUR scale includes assessment of eye movement, reducing diagnostic error in locked-in syndrome and MCS, and enables more accurate distinction between patients in coma and patients with greater signs of recovery.	High level Strong, with moderate level of evidence (EAN: European guidelines)
The CRS-R is the scale of choice for the diagnostic classification of level of consciousness in these patients. Other instruments, such as the WHIM and the SMART, may also provide clinically relevant information. Regardless of the scale used, assessments should be performed under appropriate conditions, at different times of day, and include the responses observed during rest. In the initial phases, at least 10 assessments should be performed over a period of 2—3 weeks.	High level Grade A (RCP: British guidelines)
The fundamental element in the diagnosis of patients with prolonged DoC (UWS or MCS) is targeted clinical assessment seeking to evaluate the presence of a localisation response or behaviours clearly indicative of awareness of themselves or their environment. The diagnosis of UWS or MCS should be based on: • Assessment by trained professionals with clinical experience in the management of prolonged DoC; • under appropriate conditions; • using structured, validated assessment tools; • with serial evaluations performed during an appropriate timeframe; and in conjunction with information on potential behavioural responses recorded in the patient's clinical records or in interviews with family members/caregivers/healthcare professionals responsible for the patient's care.	High level Grade A (RCP: British guidelines)
Patients with UWS/MCS— for longer than 4 weeks are considered to present ''prolonged UWS/MCS—.'' A patient with UWS/MCS— may be considered chronic if the condition persists for: • > 3 months after a non-traumatic lesion, or • > 1 year after a traumatic lesion.	High level Grade A (RCP: British guidelines)
The follow-up and supervision of patients with prolonged DoC must consider the following premises: 1. All patients should be assigned to a professional with expertise in neurology or neurorehabilitation for follow-up or supervision. Clinical follow-up of all patients with UWS/MCS must persist at least until the situation is considered ''permanent.''	High level Grade A

Table 3 (*Continued*)

2. Patients in ''prolonged'' or ''chronic'' UWS/MCS must remain under active follow-up by a team specialised in prolonged DoC, and must be assessed at least annually, with a view to providing specialised care and monitoring any meaningful change in their level of response or clinical status. 3. These follow-up assessments must be conducted by clinicians with experience in prolonged DoC, collaborating with the responsible primary care physician, and must include, at least, the application of the CRS-R scale (with/without the WHIM). 4. At the annual follow-up assessment, all decisions must take into account the personal interest of the patient; the limitation or degree of aggressiveness of treatment must be discussed and agreed. 5. Diagnosis of permanent UWS/MCS must be confirmed by an expert on prolonged DoC. 6. From that time, it is good practice to continue following these patients up annually, for instance via telephone interviews.	(RCP: British guidelines)
After clinical stability is reached, patients with prolonged DoC must be referred to a multidisciplinary rehabilitation service with experience in the management of these patients, in order to optimise diagnostic procedures, establish prognosis, and implement an effective treatment plan.	Moderate level Grade B (AAN/ACRM: American guidelines)
Before issuing a final diagnosis, the professionals responsible for the assessment of these patients must identify and treat situations or factors that may interfere with clinical response (eg, fluctuations in level of alertness, medical problems, secondary neurological complications, sedatives, etc).	Moderate level Grade B (AAN/ACRM: American guidelines)
To reduce diagnostic errors in patients with prolonged DoC, clinical assessment must be performed by experienced professionals, and standardised instruments must be used; reassessment intervals between serial assessments must be established according to the individual clinical circumstances.	Moderate level Grade B (AAN/ACRM: American guidelines)
Patients' level of consciousness must never be classified on the basis of a single assessment. Assessments must be performed at least 5 times over a period of at least 10 days (this reduces the percentage of diagnostic errors from 36% to 5%). No reliable data are available regarding the ideal interval between assessments in the acute phase.	Moderate level Strong, with low level of evidence (EAN: European guidelines)
To improve diagnostic certainty, validated, reproducible scales must be used in patient assessments.	Moderate level Grade B (AAN/ACRM: American guidelines)
Clinicians must attempt to increase the level of alertness of patients with DoC before performing any clinical assessment of level of consciousness. Specifically designed protocols (eg, the CRS-R Arousal Facilitation Protocol) should be used for this purpose.	Moderate level Grade B (AAN/ACRM: American guidelines)
All assessments of patients with DoC must include opening of the eyes, either actively or passively, with manipulation by the therapist, in patients who do not open the eyes spontaneously or in response to stimuli. Before evaluation of signs of consciousness, the patient must receive stimulation to increase their level of alertness. The evaluation must assess the following:	Moderate level
• Resistance to opening of the eyes (a sign of preserved consciousness);	Strong, with low level of evidence
• Eye movements on the horizontal and vertical planes (detection of potential locked-in syndrome or presence of ptosis);	(EAN: European guidelines)
• Visual tracking (this may be assessed using a mirror, for instance), if the patient does not present movements on command.	

Table 3 (*Continued*)

Visual tracking should be assessed repeatedly to avoid fluctuations in level of alertness, always using a mirror. In the absence of responses to the image reflected in the mirror, photographs of the patient or close family members, or other personal items, may also be used. It is essential to rule out cortical blindness, optic nerve lesions, or oculomotor palsy that may interfere with the assessment.	Moderate level Strong, with low level of evidence (EAN: European guidelines)
Patients with DoC benefit from an optimal environment and level of stimulation. Controlled stimulation offers the greatest opportunity to observe responses to the stimuli presented. Therefore, it is important to observe the following practical advice:	Moderate level
• Healthcare professionals and family members should bear in mind that these patients often present hypersensitivity and fatigue, and overstimulation must be avoided.	Grade B
• Stimulation should primarily focus on sensations that are pleasant for the patient: their favourite music, pet animals, gentle massage, etc; stimuli must always be presented one at a time.	(RCP: British guidelines)
• Family members/friends should be asked to control their visits to avoid excessive sensory stimulation; only one or 2 visitors should be allowed at once, and visits should be short in duration.	
Clinicians must consider the possibility that patients with prolonged DoC may be experiencing pain and depression but are unable to express this. Special attention must be placed on the prevention, management, and monitoring of these symptoms, including the use of structured tools for detecting and recording their presence.	Moderate level Grade B (RCP: British guidelines)
Patients with DoC require early referral for specialist assessment.	Low level
• Patients who present DoC for longer than 72 h following a severe brain injury must be assessed by a specialist neurorehabilitation team with capacity to manage situations of high dependency.	Grade C
• Patients in whom DoC persists after the acute phase must be referred to specialist neurorehabilitation services to ensure their therapeutic needs are met.	Level E1/2 (RCP: British guidelines)
All patients with DoC and scoring $\leq$ 10 on the GCS 2 weeks after onset of coma should undergo neurological assessment during the first 3 weeks after onset, in order to:	Low level
• Confirm the cause of DoC and identify potentially reversible factors;	Grade C
• Identify underlying neurological deficits and suggest appropriate complementary examinations, if needed.	Level E1/2 (RCP: British guidelines)
In patients scoring $\leq$ 10 on the GCS 4 weeks after onset of coma, active intervention by a specialist neurorehabilitation team, led by a specialist in rehabilitation, must be requested.	Low level Grade C Level E1/2 (RCP: British guidelines)
All patients presenting altered level of consciousness lasting over 4 weeks following a severe brain injury must be referred for detailed clinical analysis at a multidisciplinary unit specialising in the evaluation and treatment of prolonged DoC.	Low level Grade C Level E1/2 (RCP: British guidelines)
All patients with DoC following TBI require regular medical and neurological assessment and periodic monitoring.	Low level Grade C (ONF: Canadian guidelines)
The following premises must be taken into account before a diagnosis of UWS or MCS is established:	Low level
• Efforts must be made to establish the cause of the brain lesion responsible for the patient's clinical condition.	Grade C
• The possibility of a reversible cause (eg, toxic substances/drugs, metabolic causes, treatable structural causes such as hydrocephalus, haemorrhage, etc) must be ruled out.	Level E1/2

Table 3 (*Continued*)

Assessment must meet the following conditions: • Environmental conditions must be appropriate (suitable position, no environmental distractions, etc). • Assessment must be performed by a professional with experience and training in DoC. • Validated tests/scales must be used, with serial recordings over a sufficient period of time. • The patient must be considered to have prolonged DoC until a definitive diagnosis is made.	(RCP: British guidelines)
During assessment, clinicians must observe any spontaneous movements and automatic motor responses that the patient presents (eg, attempts to remove tubes/sensors when agitated, scratching the nose, crossing the legs, pressing or grabbing the bedsheets or other nearby objects), as well as other movements to locate stimuli, as the presence of these signs may indicate preservation of a greater residual level of consciousness.	Low level
Some spontaneous behaviours (which are not necessarily intentional), such as automatic motor responses and certain movements in situations of psychomotor agitation, which may be observed in these patients (these may be detected objectively with such instruments as the Motor Behavior Tool or reported subjectively by family members/caregivers), have been associated with the preservation of a degree of cerebral cortical capacity.	Weak, with low level of evidence
We must always bear in mind that the appearance of conscious motor responses may be concealed or limited due to the presence of: • Cranial nerve palsy; • Quadriplegia of central or peripheral origin; • Severe spasticity; • Hypo-/bradykinesia; • Hypo-/hypertonia.	(EAN: European guidelines)
Patients' family members play a key role in the assessment of patients with DoC, as patients may respond in earlier phases if family members are present.	Low level
1. Patients' families should play an active role in the assessment and management of patients with DoC.	Grade C
2. Clinicians should work closely with patients' families, explaining: *a)* what outcomes they should seek to achieve; *b)* how to distinguish conscious responses from reflexive activity. 3. When appropriate, patients' family members should be encouraged to use such tools as the WHIM or to film the patient to record their observations.	Level E1/2 (RCP: British guidelines)
The NCS-R is recommended for regular monitoring of signs of discomfort.	Low level
1. Physicians and nurses must record signs of discomfort observed during daily care and rest.	Weak, with very low level of evidence
2. The NCS-R is highly dependent on motor skills, preservation of sensitivity, and whether or not the patient is intubated.	(EAN: European guidelines)
The assessment of these patients requires an interdisciplinary team with experience evaluating cognition, communication, and motor function in patients with DoC.	Low level Grade C Level E1/2 (RCP: British guidelines)
All patients with DoC must be periodically re-evaluated during the first year after injury by a specialised interdisciplinary team with experience in TBI.	Low level
The team must include the following professionals: intensivist, neurologist, neurosurgeon, physiatrist, physiotherapist, dietician, respiratory therapist, occupational therapist, neuropsychologist, social worker, speech therapist, etc.	High grade of recommendation with low level of evidence (ONF: Canadian guidelines)
The use of scales to evaluate delirium/confusional state (eg, the CAM-ICU) is not recommended in patients with DoC in the ICU. Patients with severe brain damage and suspected delirium/confusional state would benefit from a more detailed neurological examination, including the CRS-R, rather than other scales for assessing delirium.	Low level Weak, with very low level of evidence (EAN: European guidelines)

Table 3 (*Continued*)

Patients with DoC should undergo immediate medical and physical re-evaluation if a decrease or unexpected change of over 2 points in GCS score is observed (or if a decrease is observed in more appropriate scales reflecting neurological status, such as the CRS-R). In the event of worsening of GCS score or unexpected progression observed after injury, patients' clinical situation should immediately be re-evaluated and/or urgent referral should be requested, according to their clinical status.	Low level Grade C Priority (ONF: Canadian guidelines)
Patients with prolonged DoC must undergo formal re-evaluation at 6 and 12 months after injury. After the first year, re-evaluations should be performed annually until recovery from DoC or the death of the patient. These follow-up assessments may be based on information gathered in interviews with family members, caregivers, or other clinical professionals, and should be recorded using the CRS-R (and/or WHIM).	Low level Grade C Level E1/2 (RCP: British guidelines)
Patients with prolonged DoC who have not been formally assessed require formal evaluation of level of consciousness to guide clinical management and inform decision-making.	Low level Grade C Level E1/2 (RCP: British guidelines)
DoC is defined as a state of impaired consciousness (eg, UWS or MCS) lasting longer than 4 weeks.	Low level Grade C Level E1/2 (RCP: British guidelines)
Patients in MCS+ for longer than 4 weeks are considered to present ''prolonged MCS+.'' MCS+ may be considered chronic if the condition persists for: • > 9 months after a non-traumatic lesion; • > 18 months after a traumatic lesion.	Low level Grade C Level E1/2 (RCP: British guidelines)
UWS/MCS may be considered ''permanent'' if recovery of consciousness is considered highly improbable. Diagnosis of ''permanent UWS/MCS'' does not have legal implications, but may be helpful in managing realistic expectations regarding recovery. Diagnosis of ''chronic UWS/MCS (−/+)'' may be considered ''permanent'' if no meaningful change (as measured with serial application of the CRS-R) is observed over a period of 6 months. This diagnosis can only be established by a qualified professional meeting criteria for ''expert in the assessment of patients with prolonged DoC.''	Low level Grade C Level E1/2 (RCP: British guidelines)
Patients with ''chronic'' prolonged DoC who have not undergone formal evaluation must be assessed to establish their level of consciousness, seeking to guide their clinical management and ensure that treatment decisions are optimally adapted to patients' interests and well-being. To avoid unnecessary hospital admissions, evaluation may be performed by a professional with experience in the assessment of these patients, and must include the following aspects: 1. History. • Confirmation of the nature and extension of the original brain injury. • Review of the patient's medication, exclusion of reversible causes, and clinical assessment of primary sensory pathways. 2. Evaluation of level of consciousness. • Ideally, a score of at least 6 on the CRS-R (and/or WHIM), administered by rehabilitation or nursing staff, is required before the diagnosis can be issued. • If this is not possible, a structured interview with the patient's family or caregiver should be held to complete the CRS-R, based on the behaviours identified in the past month. • In the event of uncertainties regarding the patient's level of consciousness that may significantly affect treatment decisions, a short hospitalisation will be required.	Low level Grade C Level E1/2 (RCP: British guidelines)

Table 3 (*Continued*)

Proper assessment of patients with DoC must meet the following conditions: 1. Structured assessment tools must be used (standardised, validated scales). 2. Assessment must never be based on a single examination, but rather requires careful observation over a sufficient period of time. 3. Assessment should include patients' family members/close friends, whose presence may increase the likelihood of early responses.	Low level Grade C Level E1/2 (RCP: British guidelines)
In the event of persistent uncertainty about the evidence of consciousness despite repeated clinical assessments aiming to detect behavioural changes, or if confounding factors are identified that may limit the validity of the clinical diagnosis, clinicians should perform multimodal assessments including complementary studies, such as specialised functional neuroimaging or electrophysiological studies, in order to evaluate the evidence of signs of consciousness that were not detected in the clinical assessment and which may support an alternative diagnosis.	Low level Grade C (AAN/ACRM: American guidelines)
Specialised programmes for the diagnostic assessment and prognostic estimation of DoC must follow a systematic approach, based on a thorough review of the patient's clinical record, recent structural neuroimaging data, and the results of clinical assessments, which must be performed repeatedly and be based on validated measurement scales.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Differential diagnosis between different entities on the DoC spectrum (coma, VS/UWS, MCS) must be based on the information published in evidence-based guidelines, following diagnostic procedures with recognised reproducibility and reliability, and must rule out the confounding factors frequently observed in this population, such as the effect of sedative treatment or the presence of underlying motor, cognitive, or sensory deficits.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
When communicating matters related to diagnosis or prognosis to patients' family members, caregivers, or other professionals, effort must be made to ensure that they are able to understand the clinical information provided (including diagnostic characteristics and prognostic indicators), which must include the degree of certainty of the information, according to the best available level of evidence.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
At admission, a complete neurosensory examination must be performed to evaluate the possibility of auditory, visual, sensory, or motor deficits that may previously have gone undetected; pharmacological treatments must be reviewed to avoid and, where possible, replace drugs with greater sedative potential; and imaging tests must be reviewed, and repeated if necessary, in order to define residual lesions and detect any late complications.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
When assessing level of alertness and the different clinical responses observed in the patient, the effect on these of any environmental factors (eg, body position, lighting, time of day, level of stimulation, presence of distractions, restraints, etc) must be taken into account.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Patient follow-up must be conducted on an individual basis, using validated measures of clinical status, level of response at onset, pathway and rate of recovery, level of disability, and individual treatment response. Assessments should be conducted and their results reviewed with sufficient frequency to respond to relevant questions that arise.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
The diagnostic study to identify treatable causes of brain damage responsible for the DoC must include: • An imaging study (CT or MRI) to rule out the possibility of a haemorrhage or potential hydrocephalus, if these studies were not performed in the acute phase.	Low level Grade C

Table 3 (*Continued*)

• Clinical assessment to confirm that the primary somatosensory, visual, auditory, and motor pathways are intact. If there is suspicion that one or more neurological pathways are compromised, diagnosis may be completed with the standard EEG response to eye opening or with visual, auditory, or sensory evoked potentials. However, EEG is not part of the standard clinical assessment, except in cases of suspected subclinical (non-convulsive) seizures.	Level E1/2
• A targeted diagnostic study to rule out metabolic/infectious disorders.	(RCP: British guidelines)
• Review of the patient's pharmacological treatments in order to suspend or withdraw any drug that may affect level of alertness, unless essential.	

AAN: American Academy of Neurology; ACRM: American Congress of Rehabilitation Medicine; CAM-ICU: Confusion Assessment Method for the ICU; CRS-R: Coma Recovery Scale-Revised; CT: computed tomography; DoC: disorder of consciousness; EAN: European Academy of Neurology; FOUR: Full Outline of Unresponsiveness; GCS: Glasgow Coma Scale; ICU: intensive care unit; MCS: minimally conscious state; MRI: magnetic resonance imaging; NCS-R: Nociception Coma Scale-Revised; NIDILRR-TBIMS: National Institute on Disability, Independent Living and Rehabilitation Research (Traumatic Brain Injury Model Systems); ONF: Ontario Neurotrauma Foundation; RCP: Royal College of Physicians; SMART: Sensory Modality Assessment and Rehabilitation Technique; TBI: traumatic brain injury; UWS: unresponsive wakefulness syndrome; VS: vegetative state; WHIM: Wessex Head Injury Matrix.

it is essential to conduct exhaustive, repeated evaluation of the potential presence of visual problems, to ensure eyes are open during assessment, and to specifically assess visual fixation and tracking, on both the horizontal and the vertical planes (using a mirror or personalised objects/images, if necessary).

Recommendation 6 (level of agreement: 100%, score: 8.3/9)

Wherever possible, presence of pain should be evaluated; we recommend the use of scales adapted to this population, such as the Nociception Coma Scale-Revised (NCS-R).

Recommendation 7 (level of agreement: 100%, score: 9/9)

Assessment must take into account potential confounding factors that may interfere in the evaluation or modify the observable clinical responses; these include the effects of potentially sedative medications or other reversible, treatable causes of impaired consciousness (toxic substances, recreational drugs, etc), as well as medical (metabolic causes, infectious processes, etc) or neurological complications (particularly the presence of motor alterations or seizures; however, it is also important to rule out cranial nerve alterations or cognitive, communication, or sensory deficits).

Recommendation 8 (level of agreement: 100%, score: 8.8/9)

Assessment must take into account potential environmental distractions (body position, lighting, noise, temperature, etc) that may decrease the number or quality or responses.

Recommendation 9 (level of agreement: 100%, score: 8.7/9)

Before performing a structured assessment, clinicians should seek to establish an interaction with the patient, aiming to increase their level of alertness (using such protocols as that described in the CRS-R, for instance), and must always bear in mind the need to avoid overstimulation, which may affect the number or quality of responses during the assessment.

Recommendation 10 (level of agreement: 100%, score: 8.7/9)

Evaluation must take into account information shared by family members and other people close to the patient, as they may provide relevant emotional stimulation to the patient, which is not usually included in standardised scales.

Recommendation 11 (level of agreement: 100%, score: 8.8/9)

Evaluation must also take into account spontaneous movements and automatic motor responses (which are not necessarily intentional) that these patients may present (eg, attempts to remove tubes/sensors when agitated, scratching the face, limb movements such as crossing the legs or pressing/grabbing bedsheets or other nearby objects, etc), as well as any other movement to locate stimuli, which may indicate an uncertain degree of preserved consciousness.

When these patients should be assessed

Recommendation 12 (level of agreement: 100%, score: 9/9)

Clinical assessment including the aspects mentioned above must be part of the standard protocol for the evaluation of patients with DoC beginning in the acute phase, in order to guide their clinical management and inform decision-making.

Recommendation 13 (level of agreement: 100%, score: 8.7/9)

Clinical assessment including the aspects mentioned above must be performed repeatedly, allowing sufficient rest to prevent fatigue due to overstimulation (a minimum of 5 assessments over an approximate period of 10—21 days is recommended before an initial clinical diagnosis is established). In any case, a definitive diagnosis must never be established based on the results of a single assessment.

Recommendation 14 (level of agreement: 100%, score: 8.5—9)

During the acute phase, the interval between assessments should be established on an individual basis in accordance with the proposed objectives, with at least sufficient frequency to establish the recovery pathway (if any) or individual response to treatment (if applicable). Following diagnosis of prolonged DoC (>4 weeks since onset), assessment must be performed at least at one month and at 3, 6, and 12 months after onset; subsequently, assessment must

be performed annually or in the event of any substantial change (improvement or worsening) in the patient's clinical status.

Complementary testing. What complementary examinations should be performed in the assessment of these patients?

Table 4 summarises the main recommendations extracted from the selected CPGs regarding the complementary testing of patients with DoC, presented according to level of evidence.

Recommendation 15 (level of agreement: 90%, score: 8.3/9)

Relevant complementary examinations include some structural (MRI) or functional neuroimaging techniques (fMRI and PET) and neurophysiological examinations (EEG, q-EEG, auditory evoked potentials, visual evoked potentials, somatosensory evoked potentials, P300, mismatch negativity). Though they cannot replace clinical information, they are considered helpful for:

1 Complemnting information from clinical assessment (eg, to determine the nature and extension of the brain lesion causing DoC);
2 Assisting in the diagnosis of cases in which clinical information is unclear (eg, in identifying sensory deficits or potential neurological deficits that may affect the clinical responses observed);
3 Diagnosing suspected intercurrent processes that may be exacerbating or causing the patient's clinical situation (eg, standard EEG background activity and reactivity to rule out nonconvulsive status epilepticus, CT/MRI to rule out active hydrocephalus, etc).

Recommendation 16 (level of agreement: 100%, score: 8.3/9)

Functional paradigms for detecting cases of covert consciousness/cognitive-motor dissociation, with the use of EEG, fMRI, or PET studies, or such other techniques as TMS-EEG paradigms, cannot replace clinical diagnosis. These techniques may be used by expert teams to aid in diagnosis, particularly in patients with a clinical diagnosis of VS/UWS or MCS, in whom it can be difficult to detect signs of interaction with the environment using clinical scales; the reported sensitivity/specificity and clinical value of these tests must always be considered.

Prognosis. What is the prognosis in terms of mortality, recovery of consciousness, and functional status? What predictive variables have been identified for each of these aspects?

Table 5 includes the main recommendations extracted from the selected CPGs regarding the prognosis of patients with DoC, presented according to level of evidence.

Recommendation 17 (level of agreement: 100%, score: 9/9)

Beginning in the acute phase, the best available clinical evidence must always be taken into account when establishing the prognosis of patients with DoC.

Recommendation 18 (level of agreement: 100%, score: 8.7/9)

Insofar as is possible, predictions must always be accompanied with a degree of accuracy or certainty, as per the existing guidelines; we must also take into account the individual variability in outcomes with respect to the findings of studies of groups of patients.

Recommendation 19 (level of agreement: 100%, score: 9/9)

Patients' families or caregivers, as well as other professionals, must be regularly informed of matters related to prognosis, and clinicians must ensure that they are able to understand the clinical information provided.

Predictors

Recommendation 20 (level of agreement: 100%, score: 8.6/9)

Clinical predictors traditionally associated with better prognosis are age (better prognosis in younger patients), aetiology (cases secondary to traumatic brain injury present better prognosis than other aetiologies), and chronicity (greater likelihood of recovery in patients with shorter DoC progression times).

Recommendation 21 (level of agreement: 100%, score: 9/9)

The patient's clinical situation, and particularly scores on assessment scales, the change over time in these scores, and the quality and quantity of responses observed on these scales (visual, auditory, motor, communicative, etc) are highly relevant in prognosis.

Recommendation 22 (level of agreement: 100%, score: 8.9/9)

Overall, patients in MCS+ tend to have better outcomes than those in MCS—; the latter, in turn, tend to have better recovery prognosis than those in VS/UWS. Nonetheless, it should be noted that patients with DoC may fluctuate between these diagnostic categories, particularly at earlier stages.

Recommendation 23 (level of agreement: 100%, score: 8.4/9)

Information from certain complementary studies (extension of perfusion on SPECT, level of metabolism on PET, lesion extension and localisation in neuroimaging studies, EEG pattern and reactivity, latency and intensity of somatosensory evoked potentials, activity in active/passive paradigms in fMRI/EEG studies, P300, and/or mismatch negativity) cannot replace clinical information, but may be useful for increasing the level of certainty when establishing the prognosis.

Prediction of outcomes

Recommendation 24 (level of agreement: 100%, score: 8.6/9)

Although cases exist of late recovery of consciousness (> 3 months after injury in non-traumatic cases and > 12 months in traumatic cases), these are usually associated with prolonged functional dependence on a second person.

Table 4 Complementary testing of patients with disorders of consciousness. Summary of recommendations from the guidelines reviewed, according to level/grade of evidence.

Visual analysis of standard EEG presents high specificity but low sensitivity for detecting adequate level of consciousness.	Moderate level
1. Standard EEG provides data to complement information from clinical and neuroimaging assessment of patients with DoC. This technique is essential to rule out non-convulsive status epilepticus. 2. Special emphasis must be placed on the analysis of background activity and reactivity to external stimuli. A reactive alpha rhythm probably rules out UWS, and is associated with favourable progression. 3. Absence of bioelectrical activity in an unsedated patient on standard EEG under optimal technical conditions is incompatible with preserved level of consciousness.	Strong, with low quality of evidence (EAN: European guidelines)
In the event that uncertainty persists about the presence of clinical responses or observable behavioural changes despite repeated clinical assessments, or if confounding factors are identified that may limit the validity of the clinical diagnosis, clinicians must perform multimodal assessments including complementary studies, such as specialised functional neuroimaging or electrophysiological studies, in order to evaluate evidence of signs of consciousness that were not detected in the clinical assessment and which may support an alternative diagnosis.	Low level Grade C (AAN/ACRM: American guidelines)
In cases in which clinical examination reveals no evidence of conscious responses, but neuroimaging or neurophysiological studies do suggest preserved consciousness, the patient should be re-evaluated periodically to identify emerging signs of consciousness. In individuals who are undergoing an active programme of rehabilitation, decisions related to the reduction of rehabilitation treatment intensity should be postponed until an agreement is reached between the professionals responsible for rehabilitation of the patient and those responsible for the patient's healthcare, in the light of the lack of evidence in the patient's diagnosis.	Low level Grade C (AAN/ACRM: American guidelines)
Whenever a structural MRI is requested as a complementary examination, we suggest that resting fMRI sequences (network study) also be added as part of the patient's multimodal examination.	Low level
1. Resting fMRI can provide valuable information in these patients, although results may be affected both by sedation and by motion artefacts. 2. The default mode network is only one of multiple networks that may be used to complement the information from clinical assessment of patients with DoC. If possible, other functional networks should also be considered, such as the auditory, salience, executive, and frontoparietal networks. 3. Due to the small effect size and the heterogeneity of paradigms, the use of passive paradigms is limited to research protocols.	Weak, with low level of evidence (EAN: European guidelines)
In patients unable to respond to commands in the bedside clinical assessment, fMRI with active paradigms should be considered as part of the multimodal evaluation.	Low level
1. Active paradigms enable identification of an important, specific group of patients who are able to follow instructions despite the absence of any behavioural response in the bedside clinical assessment (eg, patients with cognitive-motor dissociation or covert consciousness). 2. It should be noted that sedation and such cognitive deficits as language alterations may act as confounding factors, and that the failure to follow commands in the bedside examination does not indicate lack of consciousness. 3. Active fMRI paradigms present high specificity but very poor sensitivity for detecting ''covert consciousness.''	Weak, with moderate level of evidence (EAN: European guidelines)
Meaningful stimuli should be used in patients with DoC undergoing fMRI studies.	Low level Weak, with low level of evidence (EAN: European guidelines)

Table 4 (*Continued*)

There is no evidence supporting non-visual (eg, quantitative) analysis of standard EEG traces for distinguishing between UWS and MCS.	Low level Weak, with very low level of evidence (EAN: European guidelines)
Sleeping EEG may be used as part of the multimodal evaluation to differentiate UWS from MCS. 1. Presence of slow waves during sleep or REM sleep are potentially more accurate than sleep spindles for differentiating between UWS and MCS. 2. Analysis of sleeping EEG with machine learning techniques may improve diagnostic accuracy.	Low level Weak, with low level of evidence (EAN: European guidelines)
Quantitative analysis of high-density EEG may be used as part of a multimodal examination to differentiate UWS from MCS. 1. Results from the use of machine learning techniques and similar algorithms seem promising. 2. Active high-density EEG paradigms enable identification of a specific, important group of patients who are able to follow commands despite the lack of evidence of a response in bedside evaluation (eg, cognitive-motor dissociation, covert consciousness, etc). 3. High-density EEG paradigms present high specificity but very poor sensitivity for detecting ''covert consciousness.'' 4. Instead of maximising the number of electrodes, future studies with high-density EEG should seek to redefine paradigms, including new, better optimised statistical analyses, if possible.	Low level Weak, with moderate level of evidence (EAN: European guidelines)
Cognitive evoked potentials may be considered for use as part of the multimodal evaluation to differentiate UWS from MCS. 1. P300 seems to be more precise than mismatch negativity for differentiating between UWS and MCS. 2. All cognitive potentials present low sensitivity, even in healthy individuals. 3. In addition to visual analysis, assessment of evoked potentials should include statistical analysis, including machine learning techniques and similar algorithms.	Low level Weak, with low level of evidence (EAN: European guidelines)
TMS-EEG paradigms should be considered as part of the multimodal evaluation to differentiate UWS from MCS. Current evidence suggests that TMS-EEG presents high sensitivity and specificity for differentiating UWS from MCS, and may play an important role in the future.	Low level Weak, with low level of evidence (EAN: European guidelines)
Resting state FDG-PET should be considered as part of the multimodal assessment of patients without observable conscious responses. Resting state FDG-PET presents high sensitivity and specificity for differentiating UWS and MCS. Clinicians must ensure that systems present sufficient technical quality, rule out potential confounding factors (diabetes, epilepsy, etc), and ensure that the patient is sufficiently alert during administration of the tracer.	Low level Weak, with low level of evidence (EAN: European guidelines)
Once the patient is diagnosed with prolonged DoC, routine neuroimaging studies are not needed. However, neuroimaging may be necessary for: • Ruling out acute or undiagnosed structural lesions. • Informing decision-making or adjusting prognosis (MRI is preferable in this case); the necessity of the study must be well justified.	Low level Grade C Level E1/2 (RCP: British guidelines)
Increased ventricle size is expected in these patients, who tend to present a high level of secondary brain atrophy, although: • In the event of clinical suspicion of treatable hydrocephalus that may be affecting the patient's responses, the neurosurgical department should be consulted. • In this group of potentially high-risk patients, it is not advisable to perform such invasive procedures as lumbar puncture in the rehabilitation setting. These procedures should be supervised by a neurosurgery team.	Low level Grade C Level E1/2 (RCP: British guidelines)

Table 4 (*Continued*)

It is unclear whether more sophisticated neurophysiological or neuroimaging studies provide better diagnostic or prognostic value beyond that of the clinical behavioural assessment.	Low level
a) These studies are not currently part of the standardised battery of assessment for patients with DoC, nor are they a legal requirement (Mental Capacity Act 2005) supporting relevant decisions.	Grade C
b) Further research is needed to understand the relationship between these complementary examinations and tests used in clinical assessment.	Level E1/2
c) In the meantime, they should only be performed in the context of research projects, and always alongside formal clinical assessment.	(RCP: British guidelines)
At admission, a complete neurosensory examination must be performed to evaluate the possibility of auditory, visual, sensory, or motor deficits that may have previously gone undetected; pharmacological treatments must be reviewed to avoid and, where possible, replace drugs with greater sedative potential; and imaging tests must be reviewed, and repeated if necessary, in order to define residual lesions and detect any late complications.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Programmes should include protocols that provide for timely medical assessment in response to a deterioration or stabilisation of the patient's clinical or functional status, or in the event of medical complications that entail a risk of worsening. During these assessments, clinicians must take into account the appearance of potential intracranial complications, non-convulsive (subclinical) seizures, occult infections, metabolic alterations, and potential adverse reactions to pharmacological treatment. Therefore, neuroimaging, neurophysiological, and laboratory studies, as well as an exhaustive review of pharmacological treatment, are generally also needed in addition to clinical assessment.	Low level Grade C (American guidelines) (ACRM/NIDILRR)

AAN: American Academy of Neurology; ACRM: American Congress of Rehabilitation Medicine; DoC: disorders of consciousness; EAN: European Academy of Neurology; EEG: electroencephalography; FDG-PET: [^{18}F]fluorodeoxyglucose positron emission tomography; fMRI: functional MRI; MCS: minimally conscious state; MRI: magnetic resonance imaging; NIDILRR-TBIMS: National Institute on Disability, Independent Living and Rehabilitation Research (Traumatic Brain Injury Model Systems); RCP: Royal College of Physicians; REM: rapid eye movements; TMS: transcranial magnetic stimulation; UWS: unresponsive wakefulness syndrome.

Recommendation 25 (level of agreement: 100%, score: 8.6/9)

Diagnosis of prolonged DoC (> 28 days) is associated with marked long-term disability. The families of these patients should receive early counselling in order to:

- Search for care resources and plan the patient's final destination, the need for caregivers, and long-term care needs;
- Complete legal procedures related to medical decision-making;
- Apply for various social/financial benefits available for disability in the corresponding settings.

Recommendation 26 (level of agreement: 100%, score: 8.8/9)

Short-/medium-/long-term mortality rates are higher in patients in VS/UWS than in those in MCS (approximately 40% vs 15% at 24 months after the initial injury, according to the most recent studies).

Recommendation 27 (level of agreement: 100%, score: 8.7/9)

In the light of numerous reports of recovery beyond 3 months after onset in VS/UWS of non-traumatic aetiology, and beyond 12 months in cases of post-traumatic aetiology, the term ''permanent'' should not be used. The term ''chronic'' should be used after this time, accompanied by the chronicity or duration of the process or the time when the lesion occurred.

Treatment. What are the main therapeutic interventions currently used in these patients, and what is their level of evidence? (Table 6)

General considerations

Recommendation 28 (level of agreement: 100%, score: 9/9)

The treatment of patients with prolonged DoC requires a transdisciplinary approach by a team of professionals with specialist training in the management of patients with complex neurological disability, including in the identification, prevention, and treatment of potential medical complications that often appear in this patient group, as well as in the assessment and follow-up of the clinical responses that these patients usually present.

Recommendation 29 (level of agreement: 100%, score: 8.8/9)

The clinicians responsible for these patients must promptly identify any advance directives and the preferences of their family members/legal representatives, and re-evaluate these periodically to guide decision-making.

Table 5 Prognosis of patients with disorders of consciousness. Summary of recommendations from the guidelines reviewed, according to level/grade of evidence.

In the first 28 days after injury, clinicians responsible for communicating with the families/caregivers of patients with DoC should avoid making statements suggesting that the prognosis in these patients is universally poor.	High level Grade A (AAN/ACRM: American guidelines)
After diagnosis of prolonged DoC, it should be noted that this diagnosis is associated with marked long-term disability. The families of these patients should therefore receive early counselling in order to: - Search for care resources and plan the final destination of the patient, the need for caregivers, and long-term care needs. - Complete legal procedures related to medical decision-making. - Apply for various social/financial benefits available for disability in the corresponding setting.	High level Grade A (AAN/ACRM: American guidelines)
Assessment of patients with prolonged DoC must be standardised, with serial assessments performed with suitable frequency to identify trends of potential prognostic relevance in the recovery pathway. In this regard, the following points must be taken into account: Patients with DoC may fluctuate between different diagnostic categories (VS/UWS and MCS), particularly in the acute stage. MCS is associated with better prognosis than VS/UWS. Patients in VS/UWS may progress to MCS over time.	Moderate level Grade B (AAN/ACRM: American guidelines)
In patients in VS/UWS of traumatic aetiology, results of the following examinations, performed in the time periods described, may have the following levels of predictive value: 1—2 months after injury: - Normal brain SPECT: associated with greater likelihood of recovery of consciousness and lower level of disability/dependence at 12 months. 6—8 weeks after injury: - MRI showing lesions to the corpus callosum, dorsolateral region of the upper brainstem, or corona radiata: associated with greater probability of persistent VS/UWS at 12 months. 2—3 months after injury: Disability Rating Scale score < 23: associated with greater probability of recovery of consciousness at 12 months.	Moderate level Grade B (AAN/ACRM: American guidelines)
In patients in VS/UWS of anoxic (not traumatic) aetiology, results of the following examinations, performed in the time periods described, may have the following levels of predictive value: - CRS-R score $\geq$ 6 at least 1 month after onset: associated with greater probability of recovery of capacity to respond to stimuli at 24 months.	Moderate level Grade B (AAN/ACRM: American guidelines)
In the light of numerous reports of recovery beyond 3 months after onset in patients in VS/UWS of non-traumatic aetiology, and beyond 12 months in cases of post-traumatic aetiology, the term ''permanent'' should not be used. The term ''chronic'' should be used after this time, accompanied by the chronicity or duration of the process.	Moderate level Grade B (AAN/ACRM: American guidelines)
Patients' families should be informed that (in general terms): - Diagnosis of MCS in the first 5 months after a traumatic lesion is associated with better recovery. - Diagnosis of VS/UWS (rather than MCS) in non-traumatic (rather than traumatic) aetiologies is associated with poorer outcomes. However, outcomes vary between individuals, and prognosis is not universally poor.	Moderate level Grade B (AAN/ACRM: American guidelines)
Patients in chronic VS/UWS (> 3 months in DoC of traumatic origin, and > 12 months in non-traumatic cases), counselling should place special emphasis on the likelihood of a prolonged situation of severe disability, which will require long-term care.	Moderate level Grade B (AAN/ACRM: American guidelines)

Table 5 (*Continued*)

In patients in VS/UWS of anoxic (not traumatic) aetiology, results of the following examinations, performed in the time periods described, may have the following levels of predictive value:	Low level
- Presence of somatosensory evoked potentials following bilateral median nerve stimulation (if possible): associated with greater probability of recovery of capacity to respond to stimuli at 24 months.	Grade C (AAN/ACRM: American guidelines)
In patients in VS/UWS of traumatic aetiology, results of the following examinations, performed in the time periods described, may have the following levels of predictive value:	Low level
2—3 months after injury: - Presence of P300 wave (if possible): associated with greater probability of recovery of consciousness at 12 months. - Presence of EEG reactivity (if possible): associated with greater probability of recovery of consciousness at 12 months. At any time after injury: - fMRI (if viable and affordable) showing significant activation of the auditory association cortex in response to a familiar voice saying the patient's name: associated with greater probability of recovery of consciousness at 12 months after the examination, in patients with UWS at 1—60 months after injury.	Grade C (AAN/ACRM: American guidelines)
Specialised programmes for the diagnostic assessment and prognostic estimation of DoC must follow a systematic approach, based on a thorough review of the patient's clinical record, recent structural neuroimaging data, and the results of clinical assessments, which must be performed repeatedly and be based on validated measurement scales.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
The best available clinical evidence must always be taken into account when establishing the prognosis of patients with DoC. When establishing prognosis, it is important to take into account the following: *1)* the predictors considered; *2)* the outcome of interest; *3)* chronicity at the time the prediction is made (eg, 2 weeks, 3 months, 60 months); *4)* the timeframe for the predicted outcome (eg, 6, 12, or 60 months) and the level of accuracy associated with the prediction.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
When communicating matters related to diagnosis or prognosis to patients' family members, caregivers, or other professionals, efforts must be made to ensure that they are able to understand the clinical information provided (including diagnostic characteristics and prognostic indicators), which must include the degree of certainty of the information, according to the best available level of evidence.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)

AAN: American Academy of Neurology; ACRM: American Congress of Rehabilitation Medicine; CRS-R: Coma Recovery Scale-Revised; DoC: disorders of consciousness; EEG: electroencephalography; fMRI: functional MRI; MCS: minimally conscious state; MRI: magnetic resonance imaging; NIDILRR-TBIMS: National Institute on Disability, Independent Living and Rehabilitation Research (Traumatic Brain Injury Model Systems); SPECT: single-photon emission computed tomography; UWS: unresponsive wakefulness syndrome; VS: vegetative state.

Recommendation 30 (level of agreement: 100%, score: 9/9)

The clinicians responsible for these patients must advise and inform their family members/legal representatives about the limitations of the different available treatments with regard to the level of evidence on their efficacy, and the potential risks associated with interventions lacking evidence on their use.

- When speaking about any treatment for this population, clinicians must provide patients' families/legal representatives with evidence-based information on the benefits and potential risks of a specific treatment, and the level of evidence associated with the proposed intervention. It is important to bear in mind the particular situation of vulnerability that these people find themselves in, given the severity and uncertainty of the clinical situation.
- Clinicians must advise family members that it is difficult in many cases to establish whether the improvements observed, especially in early stages of the disease, are caused by a specific intervention or by spontaneous recovery.

Recommendation 31 (level of agreement: 100%, score: 9/9)

Periodic contact must be established between the clinical team and the patient's family to provide support and facilitate a mutual exchange of information. Families must be offered a support programme including:

- Information on the patient's clinical status and prognosis, as well as the planned treatment;

Table 6 Therapeutic interventions in patients with disorders of consciousness. Summary of recommendations from the guidelines reviewed, according to level/grade of evidence.

Insufficient evidence is available to issue a formal recommendation on the use of drugs to improve patients' level of alertness/consciousness; however, the results of clinical trials suggest that some patients may benefit from amantadine during the recovery phase.	High level
1. The question of whether or not to administer a pharmacological treatment is a clinical decision that must be made jointly with patients' family members according to the greatest benefit to the patient, considering the cost-benefit balance and the evidence of efficacy. 2. If a pharmacological treatment is selected, it must be administered on the basis of a therapeutic trial, following an A-B-A design, using a single drug at a time, and always with formal clinical assessment to monitor the effects of treatment.	Grade A (RCP: British guidelines)
The clinicians responsible for these patients must promptly identify the patient's advance directives (if any) and the preferences of their family members, and re-evaluate them periodically to guide decision-making.	High level Grade A (AAN/ACRM: American guidelines)
The use of amantadine should be considered in patients in VS/UWS and/or MCS following TBI, to improve their level of alertness and consciousness and to accelerate their functional recovery.	High level Grade A Priority level (ONF: Canadian guidelines)
Patients with DoC benefit from an optimal environment and level of stimulation. Controlled stimulation provides the greatest opportunity of observing responses to the stimuli presented. The following practical advice may be helpful: • Healthcare professionals and family members should bear in mind that these patients often present hypersensitivity and fatigue, and overstimulation must be avoided. • Stimulation should primarily focus on sensations that are pleasant for the patient: their favourite music, pet animals, gentle massage, etc; stimuli must always be presented one at a time. • Family members/friends should be asked to control their visits to avoid excessive sensory stimulation; only one or 2 visitors should be allowed at once, and visits should be short in duration.	Moderate level Grade B (RCP: British guidelines)
Clinicians responsible for the care of patients with DoC must systematically monitor for the potential medical complications that typically appear in the first months after injury, enabling their prevention, identification, and early treatment. The most frequent complications are typically agitation/aggression, hypertonia, sleep alterations, and urinary tract infections. More severe complications, such as hydrocephalus, severe respiratory tract infections (pneumonia), or paroxysmal sympathetic hyperactivity may interfere with rehabilitation, often necessitating readmission.	Moderate level Grade B (AAN/ACRM: American guidelines)
The clinicians responsible for the care of patients with DoC must evaluate whether patients present signs of pain or suffering, which must be treated if there are reasonable grounds to suspect that the patient is in pain, regardless of their level of consciousness. The clinicians responsible for the care of patients with DoC must inform their family members that it is not possible to know with certainty the exact level of pain and suffering that patients in this state may be experiencing.	Moderate level Grade B (AAN/ACRM: American guidelines)
In patients with DoC (VS/UWS or MCS) of traumatic aetiology of 4—16 weeks' progression, amantadine (100—200 mg twice daily) should be prescribed to accelerate functional recovery and reduce the degree of disability in the early stages of recovery, after ensuring that the patient has no medical contraindications or other specific risks associated for the use of the drug.	Moderate level Grade B (AAN/ACRM: American guidelines)

Table 6 (*Continued*)

The clinicians responsible for these patients must advise and inform their family members about the limitations of the different available treatments in terms of level of evidence and efficacy, and the potential risks associated with interventions lacking evidence on their use.	Moderate level
a) When discussing non-validated treatments, clinicians must provide evidence-based information on the benefits and potential risks of a given treatment, and the level of uncertainty associated with the proposed intervention, taking into account the fact that patients' families/caregivers are often distressed and vulnerable. *b)* Clinicians must inform family members that it is impossible in many cases to establish whether the improvements observed, especially in early stages of the disease, are caused by a specific intervention or by spontaneous recovery.	Grade B (AAN/ACRM: American guidelines)
As soon as the clinical situation allows, patients with persistent DoC should be transferred to a neurorehabilitation unit specialising in the assessment and management of these patients.	Low level Grade C (RCP: British guidelines)
Patients with prolonged DoC require multidisciplinary management by a team of professionals with specialised training in the management of patients with complex neurological disability and in the assessment and follow-up of the clinical responses typically observed in these patients. One of the team's primary objectives must be to provide families with practical information and emotional support, and to collect all information provided by families/caregivers that may be relevant in decision-making.	Low level Grade C (RCP: British guidelines)
The rehabilitation of patients with prolonged DoC must be based on the following premises: Patients must be offered a care programme coordinated by a multidisciplinary team, including: • 24-h care including all the support needed to maximise the patient's potential for interaction. • Medical treatment of any complications derived from the brain injury. • Formal evaluation of the patient's level of interaction and degree of response to the different stimuli presented. Discharge planning must begin early, and include a formal meeting with the patient's family and clinical professionals to establish the most appropriate destination and begin discussing the patient's needs in terms of cost. Not all patients with DoC can be expected to display functional changes in the short term that will be reflected in standard progression registers. Instead, outcomes of these programmes should be assessed using such measures as Goal Achievement Scaling (GAS).	Low level Grade B (RCP: British guidelines)
In patients with DoC following TBI, a period of treatment at a specialised tertiary-level centre should be considered if local services are unable to meet the patient's specialised rehabilitation and nursing care needs.	Low level Grade C (ONF: Canadian guidelines)
The duration of the patient's stay at a specialised centre must depend on their individual needs, and is determined by the time needed to control potential clinical complications, perform formal evaluation of the level of consciousness, and prepare a suitable discharge plan. • The time needed for the patient's family to adapt to the situation must also be taken into account. • In the majority of cases, 2—4 months is sufficient time; however, periods of up to 6 months are occasionally needed, particularly in patients showing good recovery.	Low level Grade C Level E1/2 (RCP: British guidelines)
Unless advance directives are in place, all treatment decisions must take into account the greatest benefit to the patient, always respecting his/her possible wishes. 1. Decision-making begins with the premise that the best interest of the patient is the preservation of life; no treatment or intervention must be started or continued by default.	Low level Grade C

Table 6 (*Continued*)

2. Formal meetings must be held early to establish the patient's best interests, seeking consensus with the patient's family and other representatives. At these meetings, agreements must be made on: • Resuscitation in the event of cardiorespiratory arrest. • The need for urgent measures, such as transfer to an ICU if needed, or the continued administration of antibiotic treatment. • Continuity of long-term treatments, including: *a)* Preventive measures (eg, anticoagulation, tracheostomy, etc); *b)* Treatments for organ failure (eg, insulin, dialysis, etc); *c)* Enteral/parenteral nutrition. • The limitation of therapeutic interventions must be established at each stage of treatment, and reviewed regularly.	Level E1/2 (RCP: British guidelines)
Periodic contact must be established between the clinical team and the patient's family to provide support and facilitate a mutual exchange of information. Families must be offered a support programme including: *a)* Information on the patient's clinical status and prognosis, as well as the planned treatment; *b)* Emotional support; *c)* Practical information on administrative and bureaucratic procedures. Furthermore, family members must be afforded the opportunity to actively participate in decisions about the patient's interests.	Low level Grade C Level E1/2 (RCP: British guidelines)
Patients' families must be supported to actively participate in caring for the patient, if they wish, and must be informed and trained about the tasks or activities they can perform with the patient (eg, gentle massages or stretching, stimulation activities, etc).	Low level Grade C
The families of patients with prolonged DoC must be offered counselling and support once they are ready to receive it. In early stages, families are often unprepared to receive counselling; therefore, we must wait until they are ready before offering this help.	Level E1/2 (RCP: British guidelines)
Patients with DoC following TBI must be offered a progressive programme to increase tolerance to sitting and standing, provided stimulation to increase their level of alertness, and possibly to help maintain postural reflexes, bowel and bladder function, and muscle trophism and bone quality.	Low level Grade C (ONF: Canadian guidelines)
Following diagnosis of permanent DoC (VS/UWS or MCS) by an expert in these conditions: 1. The clinical team must meet with the patient's family to inform them of the diagnosis and consider the different care and treatment options. 2. The patient's interests and well-being must be formally discussed, with regard to the continuity of active treatment and life support, and (if no such measures are already in place) limitation of treatment must be agreed. 3. Therapeutic teams must not restrict themselves to continuing treatment on account of this being the easiest option. *a)* Family members must have the opportunity to discuss the withdrawal of life support treatment, including the practical, legal, and emotional aspects of this decision. *b)* The clinician responsible for the general care of the patient is obliged to raise the question, rather than waiting for the patient's family to do this. 4. If the decision is made to continue with treatment, the treatment team and family must agree: *a)* where the patient will be treated, and *b)* how treatment will be funded. 5. The agreements made must be reviewed at least once per year.	Low level Grade C Level E1/2 (RCP: British guidelines)
After the initial phase, it is beneficial to transfer patients with DoC to a suitably qualified long-term care institution, where they will continue to need a programme of maintenance therapy, with specialised follow-up to monitor for signs of recovery of consciousness.	Low level Grade C Level E1/2 (RCP: British guidelines)

Table 6 (*Continued*)

Once patients are clinically stable and their needs have been clinically assessed: *a)* Patients must be attended at a location outside the acute/post-acute care setting, until it is confirmed that they are likely to remain in VS/UWS or MCS (normally 6 months to 1 year after injury). *b)* It is generally appropriate for patients to be transferred to a long-term (residential) care centre that specifically attends to the needs of adults with complex neurological disability.	Low level Grade C Level E1/2 (RCP: British guidelines)
The long-term (residential) care centre should be staffed by experienced professionals and have the necessary equipment for the treatment of patients with complex neurological disability. This includes: *a)* An appropriate programme of maintenance treatment to manage the patient's physical disability. *b)* An appropriate setting for the application of physical stimulation to promote interaction. *c)* Continuous follow-up of the patient's level of response.	Low level Grade C Level E1/2 (RCP: British guidelines)
If the patient's family is involved in caring for the patient, ease of access for family visits is often taken into account when selecting the discharge destination. 1. Families must be allowed to participate in deciding the most appropriate destination, and their preferences must be taken into account. 2. Selection of the discharge destination must take into account the family's wishes, but the most important consideration is the patient's clinical needs and well-being. 3. Unspecialised nursing homes for elderly people must only be considered if they can be shown to meet the patient's needs and, at the same time, offer advantages in terms of proximity to the family. They must never be chosen purely due to financial considerations. 4. If a legal guardian has been officially appointed, and their competences include selecting a discharge destination, then it may be the guardian who makes this decision, and they must be included in any meeting addressing this matter. 5. If the patient has no family or the family are deemed ''inappropriate to consult,'' then a legal representative or guardian must be appointed, whose opinion will be considered in assessing the patient's well-being.	Low level Grade C Level E1/2 (RCP: British guidelines)
Long-term care must be provided in an appropriate environment, usually a specialised residential centre. 1. Patients with DoC may occasionally be treated at home; the need for intensive, specialised care must be taken into account. It is rarely feasible or practical for care to be provided at home, unless one or more family members dedicate their time exclusively to acting as the primary caregiver. 2. Residential centre staff must be suitably qualified to manage the needs of patients with prolonged DoC, including the management of: *a)* Patients with severe physical disability, including the maintenance of muscle tone and posture (including the treatment of spasticity and the prevention of muscle contractures/pressure ulcers, etc), medical oversight, etc; *b)* Enteral feeding and tracheostomy management; *c)* Adequate stimulation and continuous assessment of behavioural responses; *d)* Support for patients' family members. 3. If the residence does not have its own treatment team, healthcare services must provide a programme of maintenance therapy through visits by the local community rehabilitation team, or alternative arrangements must be made. 4. The long-term care of the patient must take into account the needs of family members and the ease of access for visits, especially if the patient responds better to family members and appears to benefit from family visits.	Low level Grade C Level E1/2 (RCP: British guidelines)
Following a period of reintegration into the community, patients may require further admissions to specialised centres in the event that: 1. The patient's level of response improves to the point that they may benefit from a specialised rehabilitation programme with specific objectives; 2. The current location is unable to satisfy the patient's care needs, and these needs must therefore be redefined or an alternative solution found;	Low level Grade C Level E1/2

Table 6 (*Continued*)

3. A specific problem arises whose management requires hospital admission (eg, severe spasticity, joint deformities, pressure ulcers, etc) or surgical treatment; 4. The patient reaches a critical point for diagnosis and decision-making and requires a brief hospitalisation to assess their level of consciousness, discuss their well-being, or to complete the processes necessary to consider the withdrawal or continuity of life support.	(RCP: British guidelines)
Rehabilitation programmes for patients with DoC must be delivered by multidisciplinary teams with experience managing brain damage, including at least the following professionals: physicians, psychologists, physiotherapists, occupational therapists, speech therapists, nurses, and social workers. The team should focus on individual transdisciplinary treatment objectives to improve the patient's health, mobility, self-care, communication, and participation.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
The physical presence, at least 5 days per week (with 24 -h on-call coverage), of a physician responsible for supervising the patient's clinical status must be ensured. In programmes including patients requiring ventilation, a pulmonologist must also be available. Furthermore, procedures must be in place to ensure that, when needed, assistance may be requested from other medical professionals from any other specialty: internal medicine, neurology, physical and rehabilitation medicine, neurosurgery, infectious diseases, ophthalmology, otorhinolaryngology. Procedures must also be in place to ensure that, where necessary, patients with more severe disease or at risk of death may be transferred urgently to an acute care unit or ICU.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Care aiming to improve patients' physical status and prevent complications must be started immediately after admission and updated at least weekly, with optimisation to decrease the burden of future care insofar as is possible. As a minimum, these procedures must aim to ensure: adequate nutrition, respiratory hygiene, and prevention of aspiration risk; management of incontinence; skin care; prevention of muscle contractures; management of body position and muscle tone; prevention of deep vein thrombosis; and optimisation of sleep-wake rhythm.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Programmes should include protocols that provide for timely medical assessment in response to a deterioration of stabilisation of the patient's clinical or functional status, or in the event of medical complications that entail a risk of worsening. During these assessments, clinicians must take into account the appearance of potential intracranial complications, non-convulsive (subclinical) seizures, occult infections, metabolic alterations, and potential adverse reactions to pharmacological treatment. Therefore, neuroimaging, neurophysiological, and laboratory studies, as well as an exhaustive review of pharmacological treatment, are generally also needed in addition to clinical assessment.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Treatment plans must prioritise any pharmacological or any other type of intervention that, after systematic review, has demonstrated efficacy in improving arousal, behavioural responses, or rate of recovery. Other interventions may be considered whose efficacy or inefficacy has not been demonstrated in this type of study, so as long as the risk of adverse reactions is low, and within an intervention design allowing reasonable, individualised assessment of the positive and negative effects of treatment.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
The possible interventions should include different strategies, technology systems, and support products, seeking both to facilitate the detection of emerging responses and to improve these responses, transforming them into more advanced functional skills, such as communication and other interactions with the patient's surroundings. A systematic approach should be employed to evaluate which products and systems are appropriate for each patient's capacities, and to assess their effectiveness.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)

Table 6 (*Continued*)

Programmes for the management of these patients should include a well-defined staff training and information plan, ensuring that the assessments and the interventions and treatment programmes designed address patients' principal needs and the concerns of caregivers/family members, and are based on the best available evidence.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Programmes developed for this population must include systems to improve their quality, based on coherent assessment tools and well-identified indicators. Quality data should be reviewed twice annually. Quality measures may include existing evaluation tools, ad hoc measures, or a combination of both. The development of quality indicators must take into account the desired patient outcome, the needs of caregivers, and the operating characteristics of the processes included in the programme.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
When the patient has shown sufficient improvement to overcome the DoC, treatment objectives should be modified to target rehabilitation, with interventions designed to promote greater independence in mobility, self-care, communication, and other functional goals.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
After an appropriate period of intervention and evaluation, clinicians should consider transferring the patient to a setting with less intensive care, when the rate of change suggests that functional skills, rehabilitation goals, and medical needs are not changing substantially or are not expected to change in the short term; the new care setting must always be able to meet the patient's care needs.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Programmes targeting these patients must include procedures to guarantee that formal or legally appointed caregivers are provided with all the necessary information to ensure the continuity of care. As a minimum, the information that must be provided includes the patient's current level of consciousness, level of functional independence, possible medical comorbidities, current treatments, necessary equipment, the caregiver's training needs, and recommendations for follow-up with the appropriate specialists.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Programmes targeting these patients must include procedures to identify the needs of caregivers and to provide them with individualised information and training of different DoCs, prognosis, care needs, estimated treatment time, financial needs, and social care resources, as well as possible discharge destinations.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Programmes targeting these patients must include procedures for in-person appointments to address the emotional, legal, and financial needs that often arise among these patients' caregivers, as well as specific plans to access any social care resources (legal, financial, medical) in patients with more intensive rehabilitation needs.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)
Programmes targeting these patients must include procedures enabling identification of the legal representatives responsible for making decisions about guardianship, limitation of life-sustaining treatment, do-not-resuscitate orders, palliative care, or the situations in which consultations must be made with the relevant ethics committee.	Low level Grade C (American guidelines) (ACRM/NIDILRR-TBIMS)

AAN: American Academy of Neurology; ACRM: American Congress of Rehabilitation Medicine; DoC: disorders of consciousness; ICU: intensive care unit; MCS: minimally conscious state; NIDILRR-TBIMS: National Institute on Disability, Independent Living and Rehabilitation Research (Traumatic Brain Injury Model Systems); ONF: Ontario Neurotrauma Foundation; RCP: Royal College of Physicians; TBI: traumatic brain injury; UWS: unresponsive wakefulness syndrome; VS: vegetative state.

- Training on the tasks and activities that they can perform with the patient;
- Emotional support;
- Practical information on administrative and bureaucratic procedures related to the care of highly dependent patients.

Recommendation 32 (level of agreement: 100%, score: 8.5/9)

After the initial phase, patients with DoC continue to need a programme of maintenance therapy and specialised follow-up, both to monitor for signs of recovery of consciousness, should they appear, and to manage other complications that frequently appear in this population.

Pharmacological interventions

Recommendation 33 (level of agreement: 100%, score: 8.7/9)

In patients with DoC (UWS or MCS) of traumatic aetiology of 4—16 weeks' progression, the available evidence is sufficient to recommend the use of amantadine (up to 200 mg twice daily, according to the published recommendations) to accelerate functional recovery and reduce the degree of disability in the early stages of recovery; clinicians must always ensure that the patient has no medical contraindications or other specific risks associated with the use of the drug.

Recommendation 34 (level of agreement: 100%, score: 8.8/9)

Several studies have shown the benefits of:

- Amantadine treatment in non-traumatic cases or beyond 4—16 weeks after onset.
- Zolpidem (trial with a single dose of 10 mg, to be continued or increased according to the results observed).
- Levodopa or dopamine agonists in patients with lesions predominantly affecting dopaminergic pathways and associated signs of parkinsonism.
- Stimulants, if the previous drugs do not have the intended effect.

However, many of these studies present poor methodological quality; therefore, we currently lack sufficient evidence to issue a formal recommendation on the use of these drugs. The selection of any of these treatments must be based on what is considered most beneficial for the patient, in coordination with the patient's family/direct legal representative. Treatment may only be started if the risk of adverse reactions is low, and within an intervention design that enables the positive and negative effects of treatment to be reasonably established on an individual basis. The points made in the ''General considerations'' section (eg, clinical experience, cost-benefit balance, potential secondary effects, evidence of effectiveness, expectation management, etc) must always be taken into account.

Recommendation 35 (level of agreement: 100%, score: 8.6/9)

The clinicians responsible for the care of patients with DoC must inform their family members that it is not possible to know with certainty the exact level of pain and suffering that patients in this state may be experiencing. In patients showing signs of pain or suffering, or if there are reasonable grounds to suspect that the patient is in pain, clinicians should propose an analgesic trial, independently of level of consciousness, always observing the recommendations made in the ''General considerations'' section.

Non-invasive stimulation

Recommendation 36 (level of agreement: 100%, score: 8.4/9)

Insufficient scientific evidence is currently available to issue a formal recommendation on the use of these techniques. In the light of their safety profile, and pending the publication of studies with greater methodological quality that may confirm their clinical value, it seems that these techniques, and particularly transcranial direct-current stimulation, can be included in the therapeutic arsenal for these patients, and particularly for patients in MCS with partial structural and functional preservation of the stimulated areas and their connections with other brain regions. The recommendations made in the ''General considerations'' section must always be observed.

Invasive stimulation and cell therapy

Recommendation 37 (level of agreement: 100%, score: 8.8/9)

Currently, these techniques can only be recommended in the context of clinical trials conducted by expert teams, under the supervision of the competent national healthcare regulators.

Other considerations

When performing any intervention, clinicians must bear in mind that patients with DoC benefit from an environment and level of stimulation that meets the following conditions:

Recommendation 38 (level of agreement: 100%, score: 8.9/9)

- Overstimulation is avoided.

Recommendation 39 (level of agreement: 100%, score: 8.7/9)

- Stimulation primarily focuses on pleasant sensations.

Recommendation 40 (level of agreement: 100%, score: 8.9/9)

- Patients are included in a progressive programme to increase tolerance to sitting and standing, enabling them to access a greater number of environmental stimuli in order to improve their level of alertness, maintain postural reflexes, gut and bladder function, muscle trophism, and bone quality.

CRediT authorship contribution statement

The coordinators (E.N. and M.D.N.) were responsible for the study design, selection of content, literature search, drafting and review of theoretical content, and organising coordination between the working group and the expert panel. The 5 members of the working group (B.M., M.O., J.O., R.L., and A.M.) were responsible for reviewing sources from the literature, and drafting the theoretical content and the provisional recommendations. The 13 members of the expert panel (J.F., R.R., T.P., M.B., C.C., A.G., C.G., A.J., C.L., S.L., R.P., M.R., and I.Q.) participated in reviewing the provisional recommendations and drafting the definitive recommendations.

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Appendix 1. Ad hoc committee created by the Spanish Society of Neurorehabilitation to draft the guidelines

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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