Istituti Clinici Scientifici Maugeri

Disordini cronici della coscienza: considerazioni mediche ed etiche

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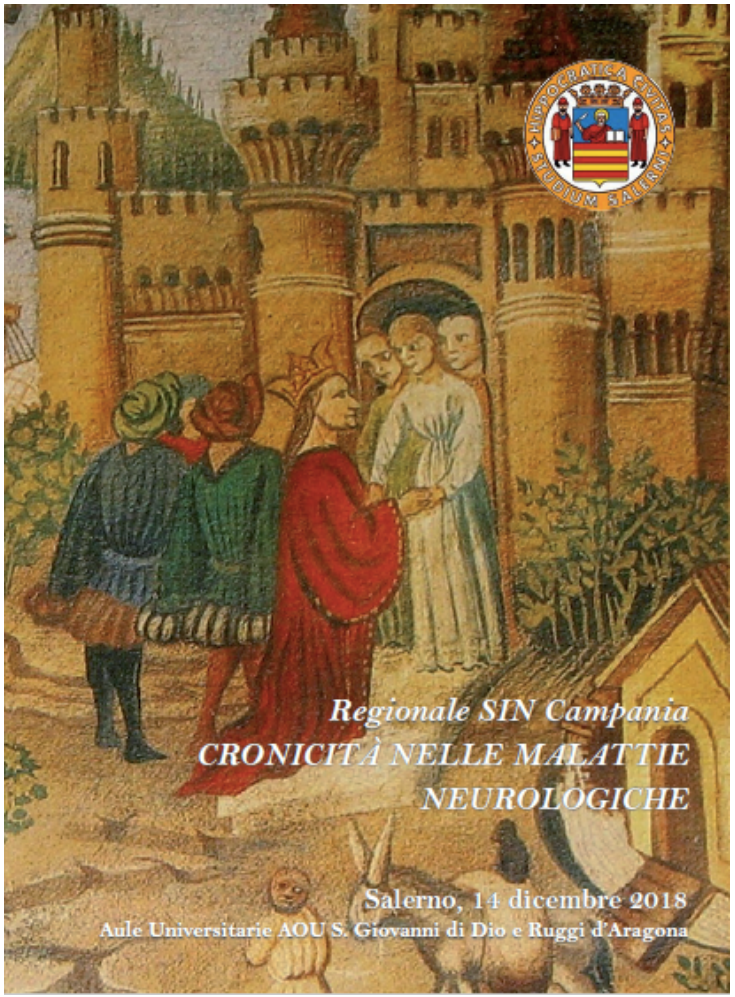

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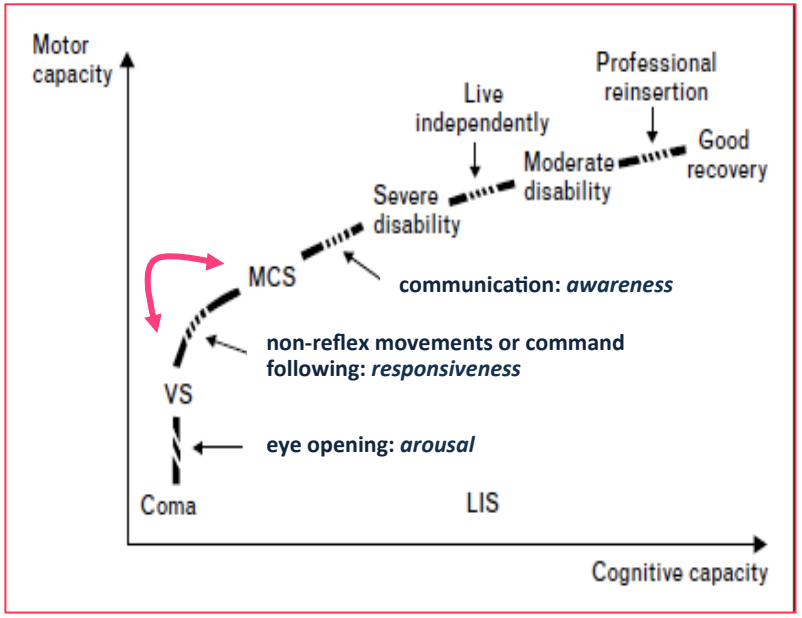
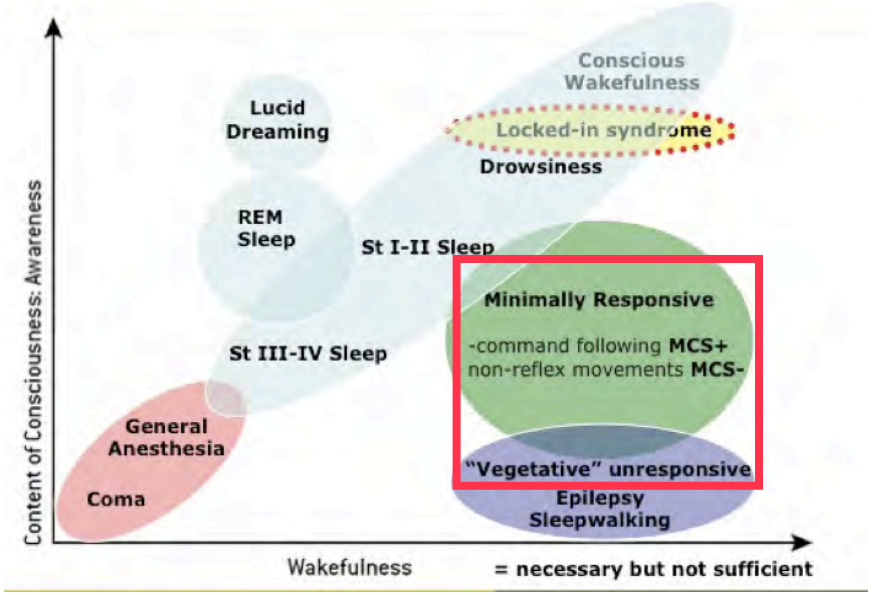
DISORDERS OF CONSCIOUSNESS



Adapted from Laureys, 2005



Laureys, 2007, 2010

Chronic unconsciousness is a tragic and ironic failure of high-technology treatment to preserve or restore brain function, the primary aim of therapeutics ***(in the acute and chronic phase)***

Bernat JL, Lancet 2006

Published Ahead of Print on August 8, 2018 as 10.1212/WNL.0000000000005926

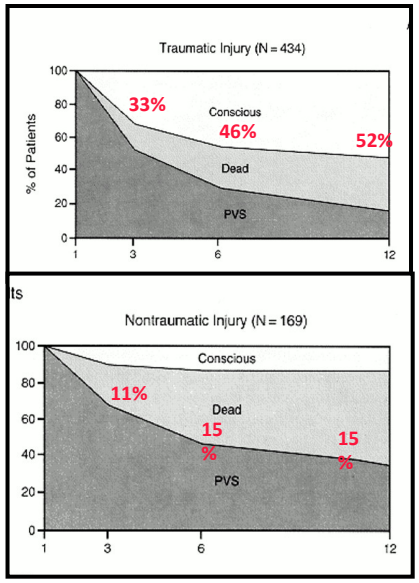
SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

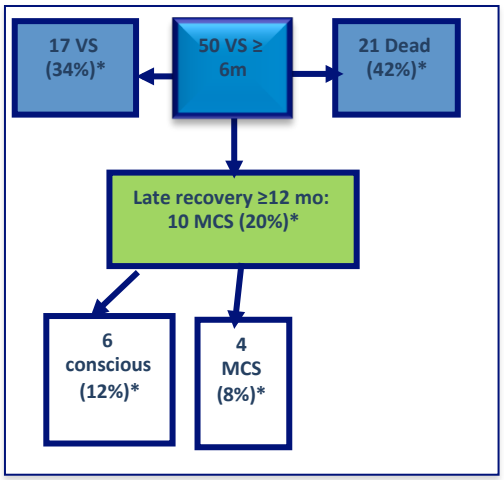
Practice guideline update recommendations summary: Disorders of consciousness

Permanent => Chronic

Persistent => Prolonged (≥28 d)



MSTF, 1994



Estraneo et al. Neurology 2010

Journal of Neurotrauma

Longitudinal Outcome of Patients with Disordered Consciousness in the NIDRR TBI Model Systems Programs

To cite this article:
Risa Nakase-Richardson, John Whyte, Joseph T. Giacino, Shital Pavawalla, Scott D.

Significant recovery continues for 2 years post-injury and to a more modest degree for as long as 5 years post injury

Recommendation 7 (Level B). Given the frequency of recovery of consciousness **after 3 months in patients in nontraumatic VS/UWS, and after 12 months in patients with traumatic VS/UWS (**including some cases emerging from MCS), use of the term permanent VS should be discontinued. After these time points, the **term chronic VS (UWS) should be applied**, accompanied by the duration of the VS/UWS

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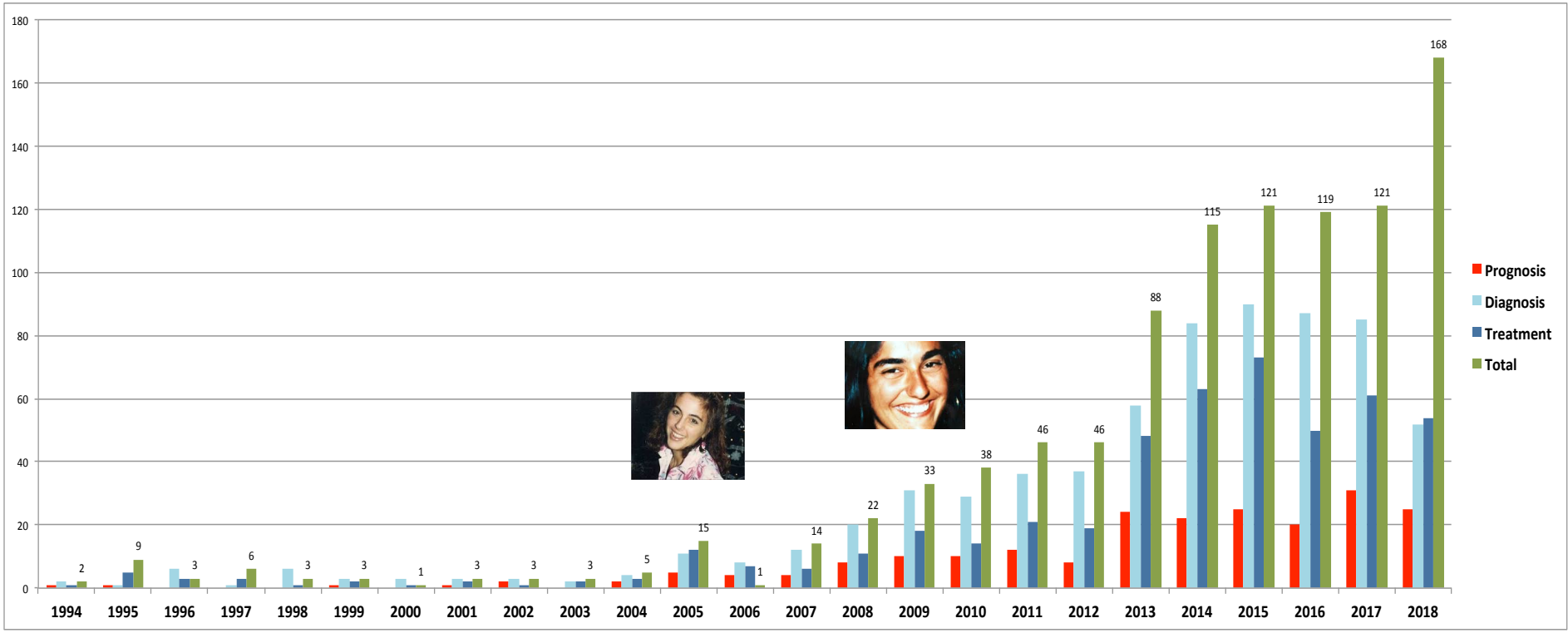
Research trend on disorders of consciousness

PubMed National Library of Medicine NLM



Therapeutic strategies for recovering consciousness

European multicenter project

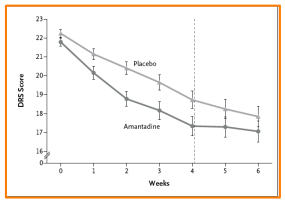
Anterior mesocircuit model

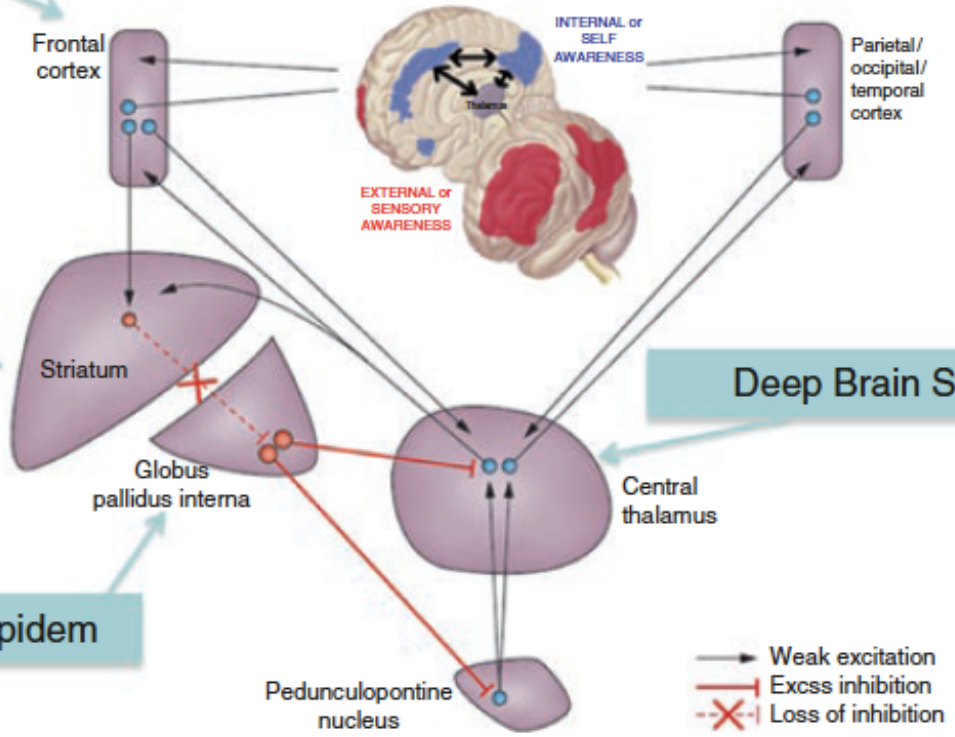
Transcraninal Direct Current Stimulation

Amantadine

Zolpidem

Deep Brain Stimulation





Giacino J, NEJM, 2012

Schiff, Trends Neurosci, 2010, Thibaut and Schiff, 2018

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Deciding the appropriate course of treatment in chronic DoC

Establishing:

- Appropriateness of different care pathways (MCS vs VS)
- Appropriateness of long-term rehabilitation treatment
- Appropriateness of therapeutic chronic management which guarantees for the patient (and their family) the maximum possible physical and mental well-being

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Deciding the appropriate course of treatment in chronic DoC

Establishing:

- Appropriateness of different care pathways (MCS vs VS)
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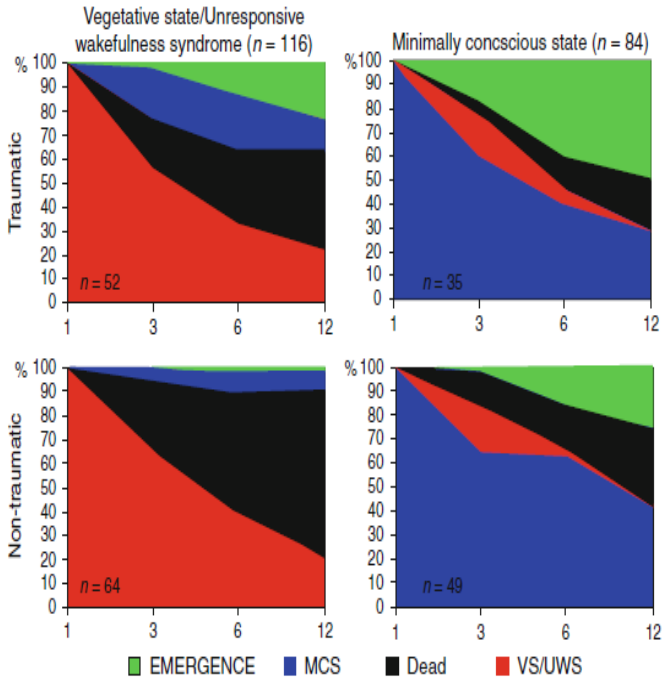
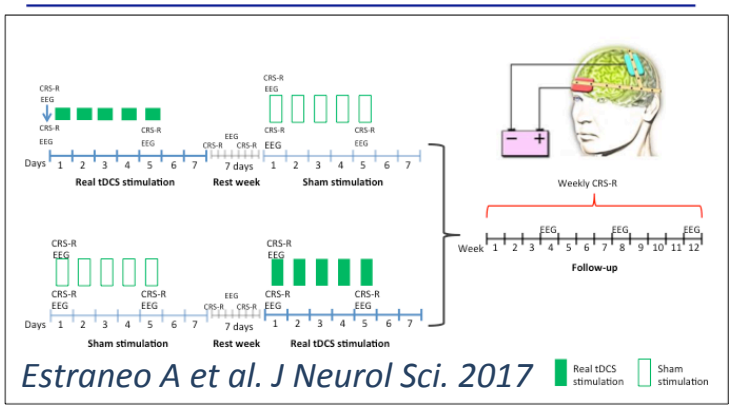
Prognosis and treatment as a function of clinical diagnosis



Bruno et al., 2012



Estraneo A et al. J Neurol Sci. 2017

Selegilina for recovery of cosnciousness in DoC

Pt.	Age at onset	Sex	Etiology	Brain lesion	Months post-onset	Contraindication for amantadine	Study entry		First change in clinical diagnosis or increase in the CRS-R arousal item			Outcome after 10-week selegiline administration		Outcome 4 weeks after selegiline withdrawal	
							Diag.	CRS-R (subscales)	Week	Diag.	CRS-R (subscales)	Diag.	CRS-R (subscales)	Diag.	CRS-R (subscales)
1*	61	F	Vascular (IH, IVH)	rTPJL rDLPFC	13	Seizures	MCS-	9 (1-1-4-1-0-2)	3	MCS+	12 (3-1-4-2-0-2)	E-MCS	20 (3-5-4-3-2-3)	E-MCS	20 (3-5-4-3-2-3)
2*	59	F	Vascular (IH; IVH)	rTPJ	9	Seizures	MCS-	9 (1-1-4-1-0-2)	6	MCS+	13 (3-3-2-2-1-2)	MCS+	15 (3-3-4-2-1-2)	MCS+	16 (3-4-4-2-1-2)
3*	24	M	Vascular (SAH)	rTPJ	8	Seizures	MCS+	9 (3-3-1-1-0-1)	8	E-MCS	16 (4-5-2-1-2-2)	E-MCS	16 (4-5-2-1-2-2)	E-MCS	16 (4-5-2-1-2-2)
4**	63	M	Vascular (IH, IVH)	rTPJ	6	Arrhythmia	VS	4 (1-1-0-1-0-1)	2	MCS+	9 (3-1-2-1-0-2)		-/-	MCS+	10 (3-1-2-1-0-2)
5	18	M	Anoxia (CA)	DA	13	-/-	MCS+	11 (3-3-2-1-0-2)			-/-	MCS+	11(3-3-2-1-0-2)	MCS+	11 (3-3-2-1-0-2)
6	18	F	Traumatic (OH)	lETP, rPO	13	Seizures	VS	7 (1-1-2-1-0-2)			-/-	VS	5 (0-0-2-1-0-2)	VS	5 (0-0-2-1-0-2)
7	49	M	Anoxia (CA)	DA, VE	12	Seizures	VS	6 (1-1-2-1-0-1)			-/-		-/-	VS	6 (1-1-2-1-0-1)
8	63	F	Vascular (IH)	rTP BG	11	Seizures	VS	5 (1-0-2-1-0-1)	3	VS	7 (1-1-2-1-0-2)		-/-	VS	7 (1-1-2-1-0-2)
9	42	F	Anoxia (RA)	DA VE	84	Seizures	VS	6 (2-0-2-1-0-1)	9	VS	7 (2-0-2-1-0-2)	VS	7 (2-0-2-1-0-2)	VS	7 (2-0-2-1-0-2)
10	27	M	Vascular (IH, IVH)	lPTO	23	Arrhythmia	VS	5 (1-0-2-1-0-1)	2	VS	6 (1-0-2-1-0-2)	VS	6 (1-0-2-1-0-2)	VS	6 (1-0-2-1-0-2)

Masotta et al., Can J Neurol Sci. 2018

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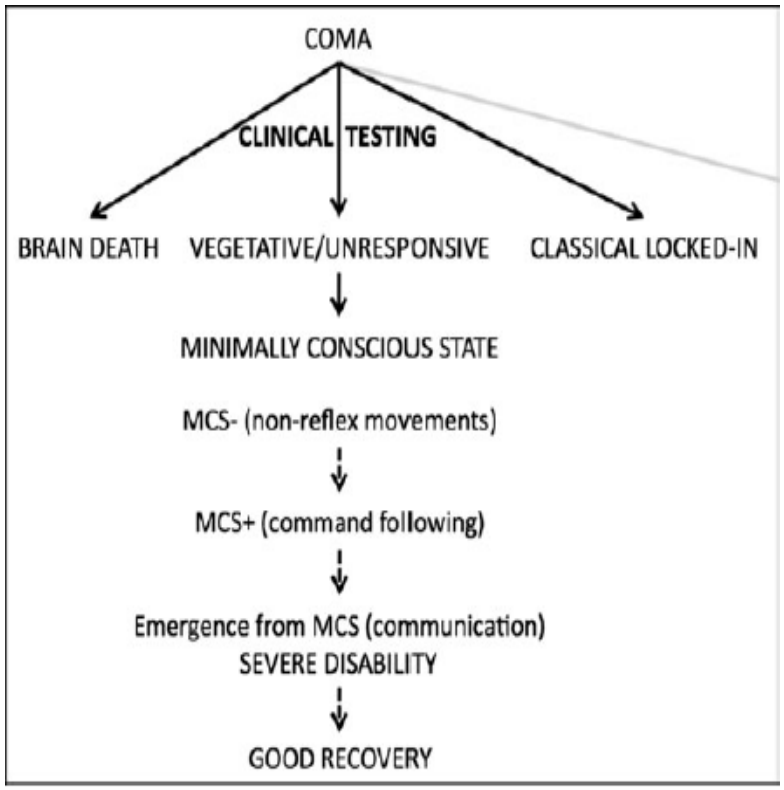
Appropriateness of different care pathways (MCS vs VS)

Diagnostic criteria of DoC



Bruno et al., 2011

VS — **MSTF 1994**

MCS- — **Giacino 2002**

MCS+ — **Bruno 2011**

Clinical diagnosis of DoC

Detection of intentional (non reflex) behavioral responses to salient stimuli by means of reliable clinical instruments

JFK COMA RECOVERY SCALE - REVISED ©2004

Record Form

This form should only be used in association with the "CRS-R ADMINISTRATION AND SCORING GUIDELINES" which provide instructions for standardized administration of the scale.

Patient:	Diagnosis:	Etiology:
Date of Onset:	Date of Admission:	

Date															
Week	ADM	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
AUDITORY FUNCTION SCALE																
4 - Consistent Movement to Command *																
3 - Reproducible Movement to Command *																
2 - Localization to Sound																
1 - Auditory Startle																
0 - None																
VISUAL FUNCTION SCALE																
5 - Object Recognition *																
4 - Object Localization: Reaching *																
3 - Visual Pursuit *																
2 - Fixation *																
1 - Visual Startle																
0 - None																
MOTOR FUNCTION SCALE																
6 - Functional Object Use †																
5 - Automatic Motor Response *																
4 - Object Manipulation *																
3 - Localization to Noxious Stimulation *																
2 - Flexion Withdrawal																
1 - Abnormal Posturing																
0 - None/Flaccid																
OROMOTOR/VERBAL FUNCTION SCALE																
3 - Intelligible Verbalization *																
2 - Vocalization/Oral Movement																
1 - Oral Reflexive Movement																
0 - None																
COMMUNICATION SCALE																
2 - Functional: Accurate †																
1 - Non-Functional: Intentional *																
0 - None																
AROUSAL SCALE																
3 - Attention																
2 - Eye Opening w/o Stimulation																
1 - Eye Opening with Stimulation																
0 - Unarousable																
TOTAL SCORE																

Denotes emergence from MCS†

Denotes MCS *

1

(Giacino et al, 2004)

BMC Neurology *2009*

BioMed Central

Research article

Open Access

Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment

Caroline Schnakers[1], Audrey Vanhaudenhuyse[1], Joseph Giacino[2], Manfredi Ventura[3], Melanie Boly[1,4], Steve Majerus[5], Gustave Moonen[4] and Steven Laureys*[1,4]

Clinical diagnosis of MCS in 41% VS patients by means of Coma Recovery Scale-Revised

Published Ahead of Print on August 8, 2018 as 10.1212/WNL.0000000000005926

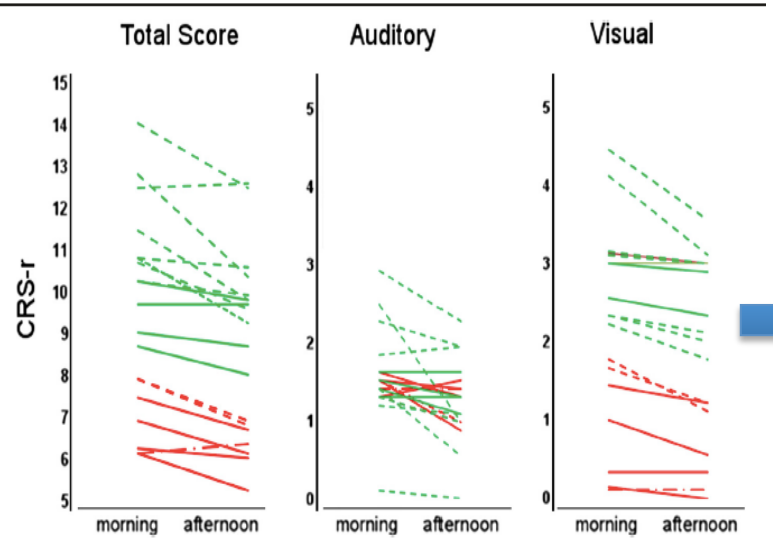
SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

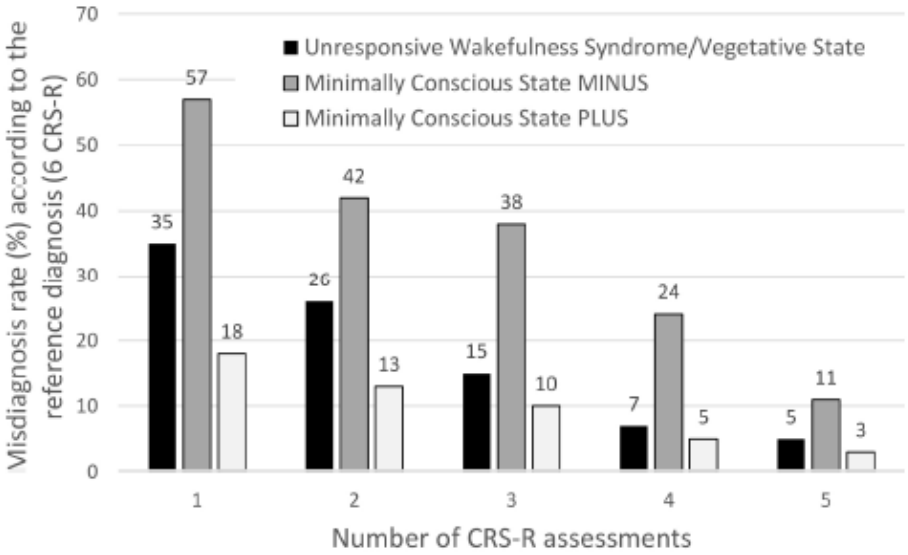
Practice guideline update recommendations summary: Disorders of consciousness

RECOMMENDED

Recommendation number	Recommendation statement and level
2b	To reduce diagnostic error in individuals with prolonged DoC after brain injury, serial standardized neurobehavioral assessments should be performed with the interval of reassessment determined by individual clinical circumstances (Level B based on cogency, feasibility, and cost relative to benefit).



Cortese et al., 2015



Wannez S. et al., 2017

Appropriateness of different care pathways (MCS vs VS)

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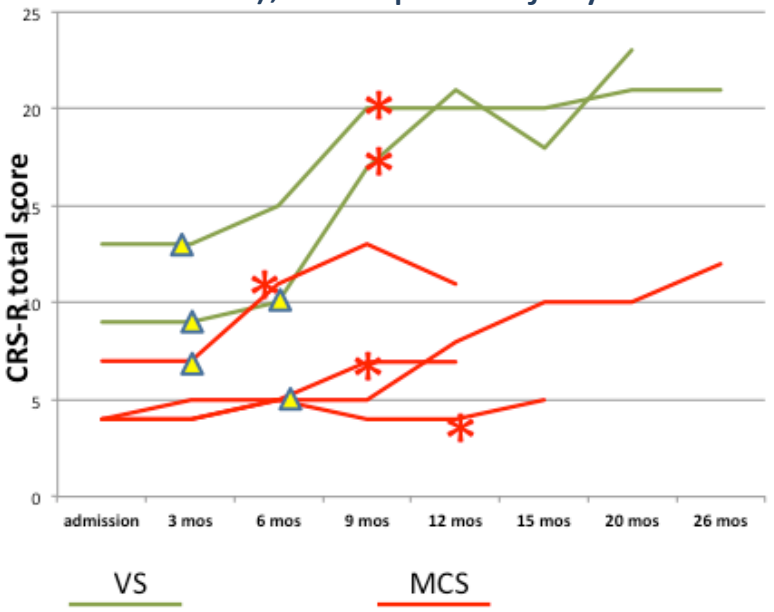
Practice guideline update recommendations summary: Disorders of consciousness

RECOMMENDED

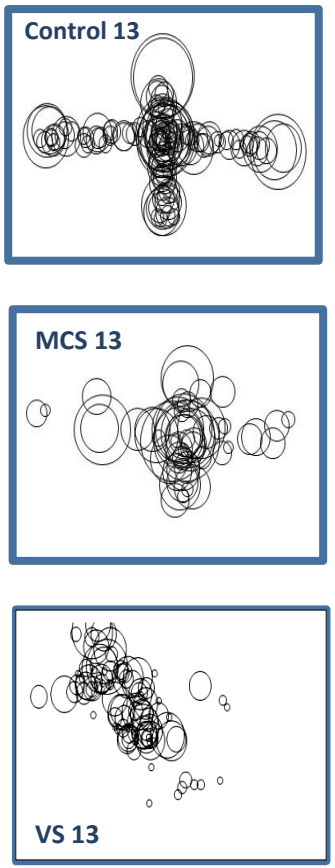
Recommendation number	Recommendation statement and level
2d	Clinicians should identify and treat conditions that may confound accurate diagnosis of a DoC prior to establishing a final diagnosis (Level B based on feasibility and cost).

VS= 4; MCS= 2 (TBI= 1, anoxic=2, vascular=3); time post-injury: 32-87 days

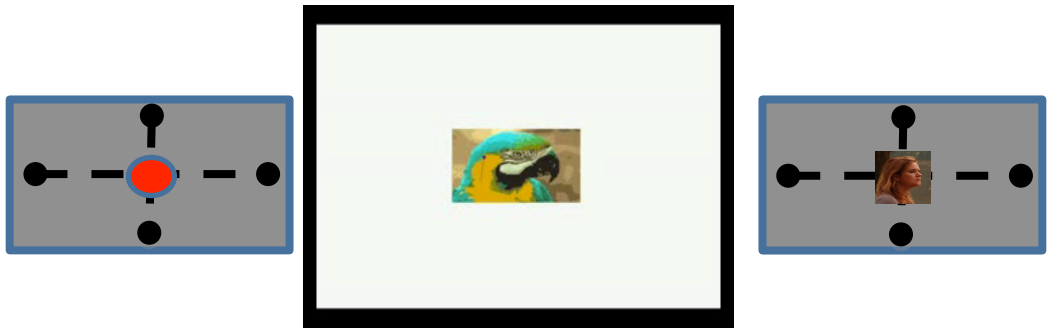


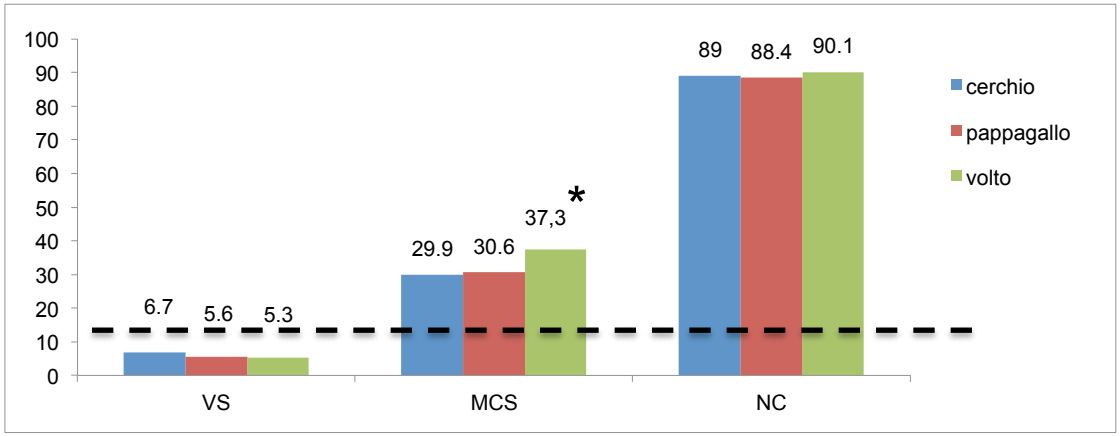
IT Baclophen effect on CRS-R total score (*not published)*

Self-referential stimuli for visual pursuit diagnosis



Trojano et al., 2012





Trojano et al., 2013

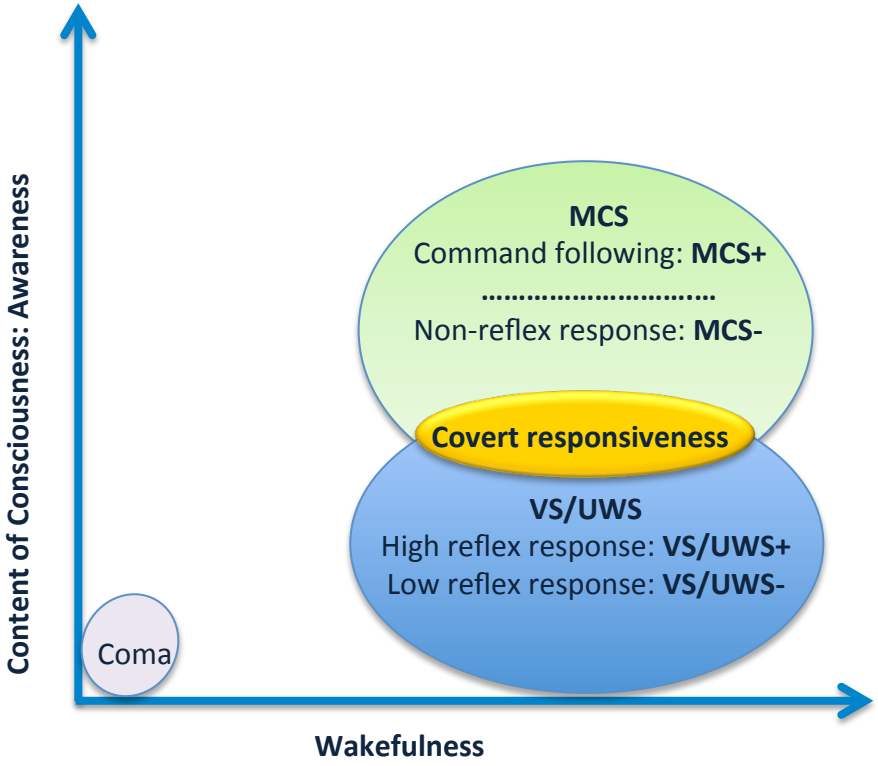
Self-referential stimuli in DoC assessment

- Patients' relatives represent emotionally salient stimuli for the patients: such stimuli can enhance cortical activation on fMR and ERP*(Di et al, 2007, Fischer et al 2006)* and elicit intentional responses *(Trojano et al, 2013)*

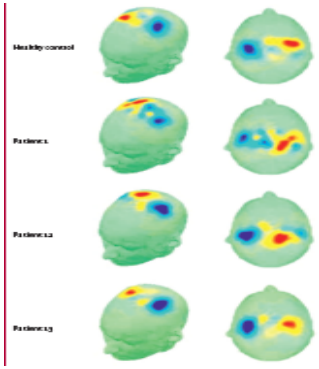
- Presence of caregivers can positively affect DoC behavioural assessments *(Formisano, 2011; Sattin , 2014)*

- If adequately trained FCs might perform long-term monitoring of patients' responsiveness *(Estraneo et al., 2010)*

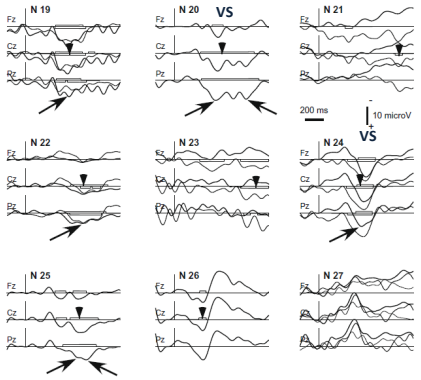
Ambigous diagnostic findings



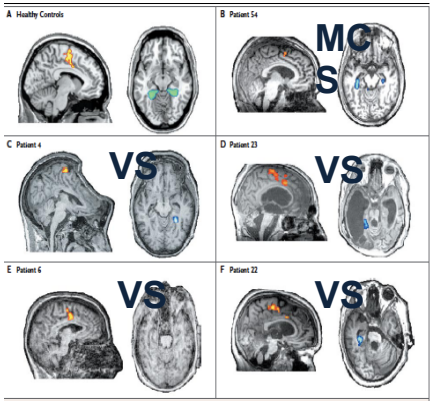
Modified from Laureys. 2005



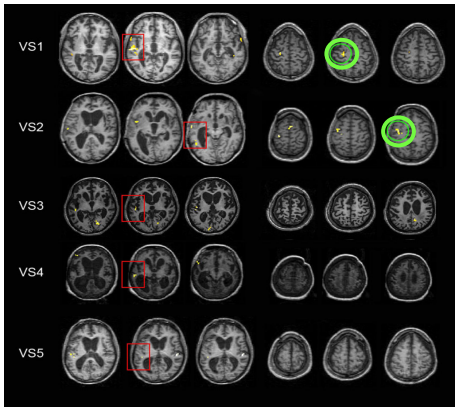
EEG response to motor imagery task. *Cruse, 2011*



P3 to the subject's own name *Fischer 2010*

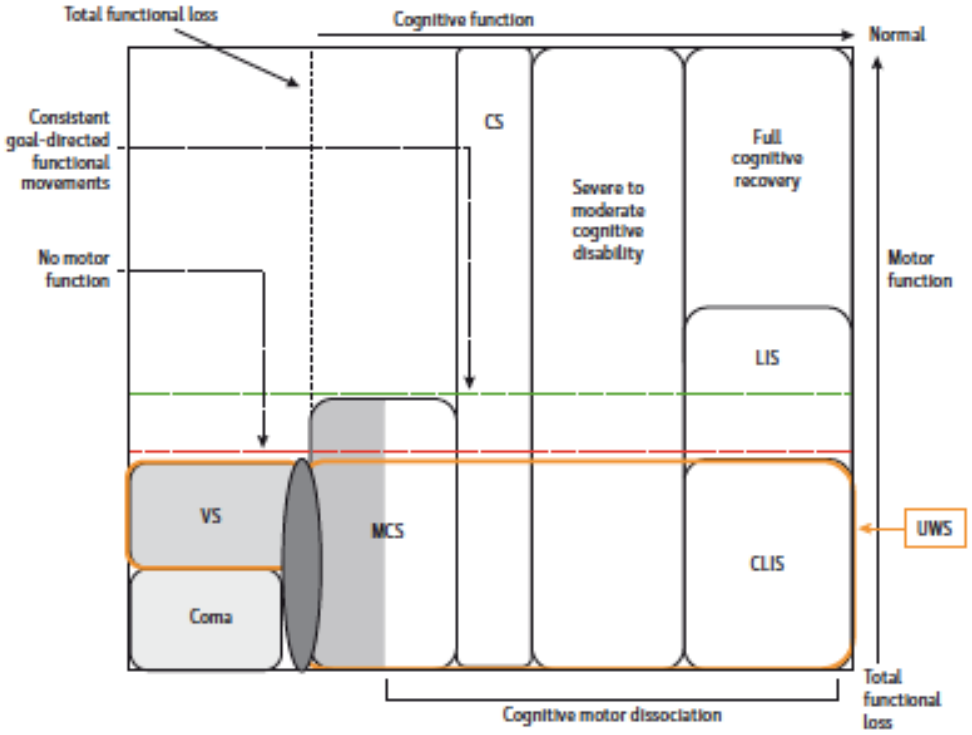


Motor or spatial imagery *Monti, 2010*

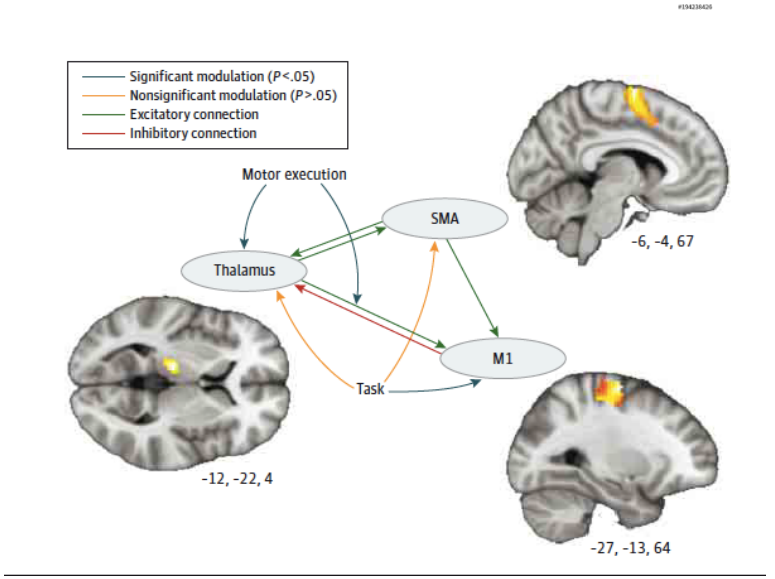


Activation to motor tasks in premotor area *Bekinschtein, 2010*

Cognitive-motor dissociation



Schiff, JAMA, 2015



Fernández-Espejo et al, *JAMA, 2015*

- ✓ Dissociation of measured bedside behavior (a lack of purposeful motor behavior) and fMRI or electrophysiologic evidence of command following
- ✓ Due to an underlying structural disruption between the motor cortex and the thalamus.

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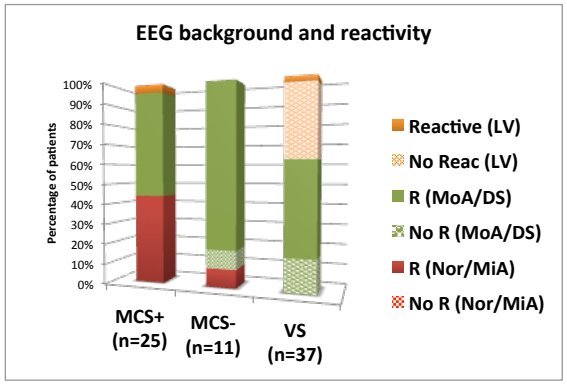
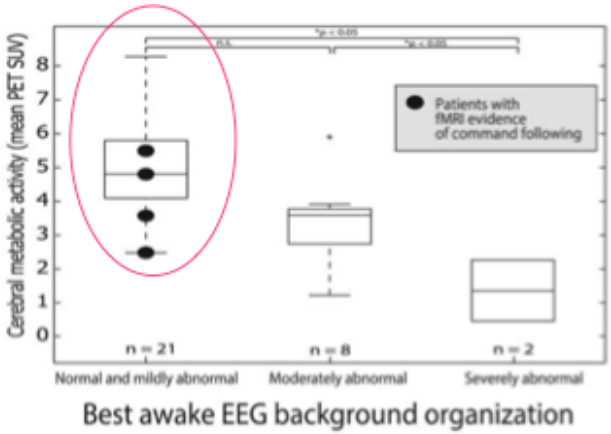
2e In situations where there is continued ambiguity regarding evidence of conscious awareness despite serial neurobehavioral assessments, or where confounders to a valid clinical diagnostic assessment are identified, clinicians may use multimodal evaluations incorporating specialized functional imaging or electrophysiologic studies to assess for evidence of awareness not identified on neurobehavioral assessment that might prompt consideration of an alternate diagnosis (Level C based on assessment of benefit relative to harm, feasibility, and cost relative to benefit).

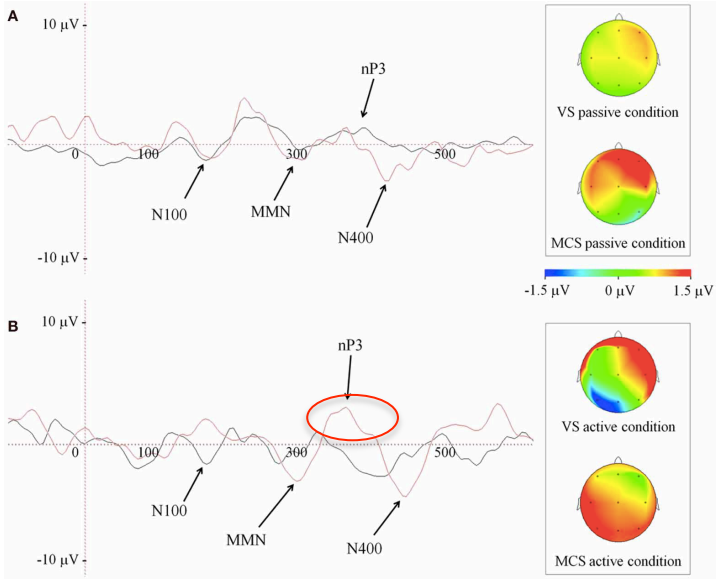


Estraneo et al., Clin Neuroph. 2016



Forgacs et al, Ann Neur, 2014

Active listening of patients'own name (nP3) in MCS



Risetti et al, 2010

Deciding the appropriate course of treatment in chronic DoC

Establishing:

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- Appropriateness of long-term rehabilitation treatment
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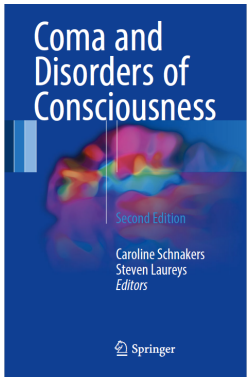
Further clinical progression in “late recovery” anoxic patients at 60-month FU

		12 – 24 months post-onset				25- 60 months post-onset		
Age at onset	**Sex**	**Dg**	**MCS (mos after onset)**	**CRS-R total score**	**DRS**	**Dg**	**CRS-R total score**	**DRS**
14	F	MCS	16	10 (2-3*-2-1-0-2)	24	Cons	23 (4*-5*-6°-3*-2°-3)	8
40	M	MCS	22	11(2-3*-2-2-0-2)	23	Cons	23 (4*-5*-6°-3*-2°-3)	10
17	M	MCS	14	10 (2-3*-2-1-0-2)	24	MCS+	16 (4*-5*-2-2-1*-2)	20
12	M	MCS	15	8 (2-2*-1-1-0-2)	24	MCS+	11 (3*-3*-2-1-0-2)	21
31	M	MCS	12	9 (2-3*-1-1-0-2)	24	MCS+	11 (3*-3*-2-1-0-2)	21
45	F	MCS	11	8 (2-2*-1-1-0-2)	24	MCS+	10 (3*-2*-2-1-0-2)	21

Estraneo et al., APMR 2014

Which factors should be considered for prognostication?

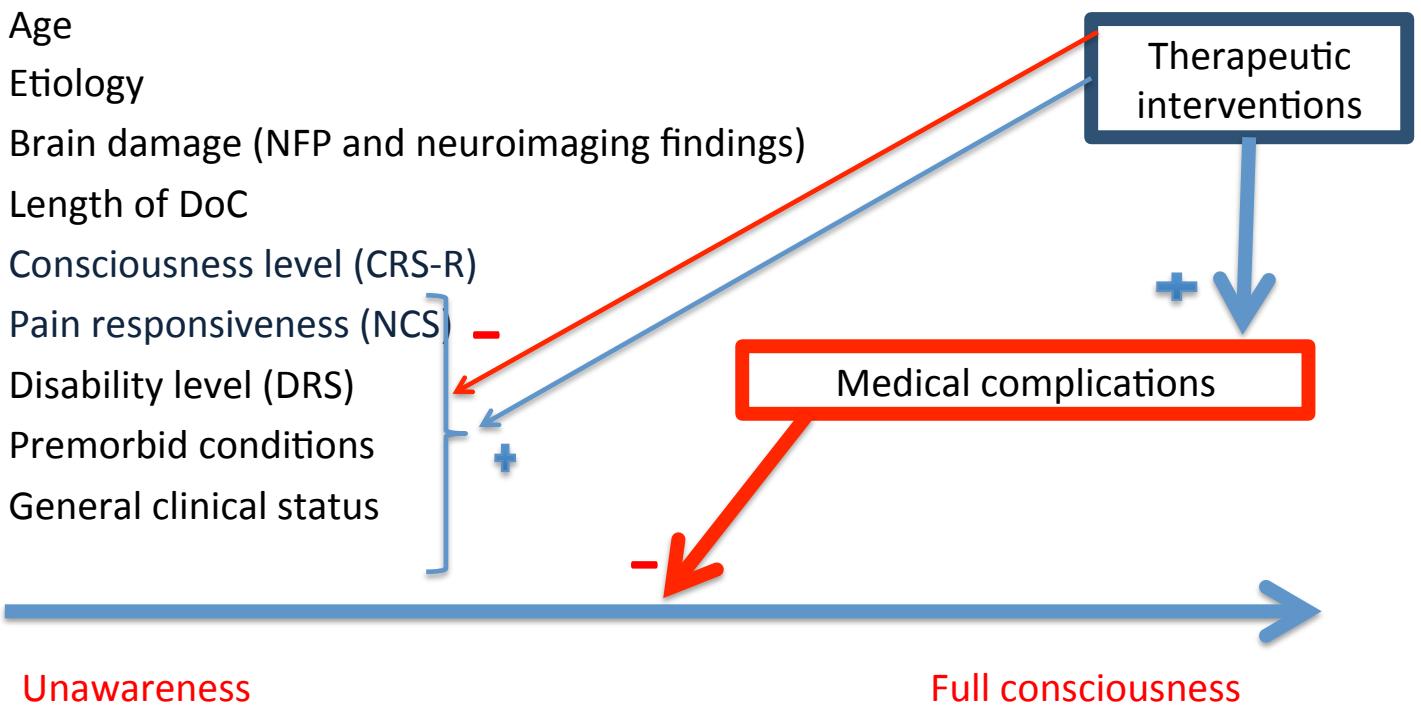


Chapter 2
Prognosis in Disorders of Consciousness

Anna Estraneo and Luigi Trojano

Abstract In patients with prolonged disorders of consciousness (DOC), clinical evolution is determined by several factors closely interacting with each other: etiology, patient's age (likely influencing the physiological process of recovery, e.g., brain plasticity), the duration of DOC (likely related to the severity of brain damage), the structural and functional integrity of neuronal populations (as assessed by neurophysiological and neuroimaging methods), and the presence of clinical complications that could impact care strategies.

In the present chapter, we will offer a brief review of the most recent studies on clinical evolution of patients with prolonged DOC and of the longitudinal studies searching for robust prognostic markers in such patients. We will argue that some prognostic indicators for patients in vegetative state can be gathered in the rehabilitative phase, whereas reliable markers to characterize DOC patients who will present late recovery of responsiveness and consciousness have not been identified. Moreover, long-term evolution of patients in minimally conscious state has not been clearly established, and definite prognostic information is not available for these patients. For these reasons, prospective longitudinal systematic investigations of outcome in large groups of individual with prolonged DOC are needed to better clarify the natural recovery of DOC and to define prognostic markers useful to update current positions on medical, ethical, and legal issues connected with management and care of these patients.



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Practice guideline update recommendations summary: Disorders of consciousness

RECOMMENDED

5	Posttraumatic VS/UWS: Clinicians should perform the DRS at 2–3 months postinjury (Level B) and may assess for the presence of P300 at 2–3 months postinjury (Level C based on feasibility) or assess EEG reactivity at 2–3 months postinjury (Level C based on feasibility) to assist in prognostication regarding 12-month recovery of consciousness for patients in traumatic VS/UWS. Clinicians should perform MRI 6–8 weeks postinjury to assess for corpus callosal lesions, dorsolateral upper brainstem injury, or corona radiata injury in order to assist in prognostication regarding remaining in PVS at 12 months for patients in traumatic VS/UWS (Level B). Clinicians should perform a SPECT scan 1–2 months postinjury to assist in prognostication regarding 12-month recovery of consciousness and degree of disability/recovery for patients in traumatic VS/UWS (Level B). Clinicians may assess for the presence of higher level activation of the auditory association cortex using BOLD fMRI in response to a familiar voice speaking the patient's name to assist in prognostication regarding 12-month (postscan) recovery of consciousness for patients in traumatic VS/UWS 1–60 months postinjury (Level C based on feasibility, cost).
6	Nontraumatic, postanoxic VS/UWS: Clinicians should perform the CRS-R (Level B) and may assess SEPs (Level C based on feasibility) to assist in prognostication regarding recovery of consciousness at 24 months for patients in nontraumatic postanoxic VS/UWS.

	reference	Odds-ratio	Lower 95%CI	Upper 95%CI	P
Age	≤50 years	.96	.65	1.06	.425
CRS-R	≥ 6	4.61	1.05	11643.58	.042
DRS	<25	0.69	.09	4.05	.585
PSH	Present	1.29	.02	972.17	.921
SEP	Present	17.88	1.37	6511.41	.026

Estraneo et al. Neurology 2013

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AMERICAN ACADEMY OF NEUROLOGY

SPECIAL ARTICLE

Practice guideline update recommendations summary: Disorders of consciousness

RECOMMENDED

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

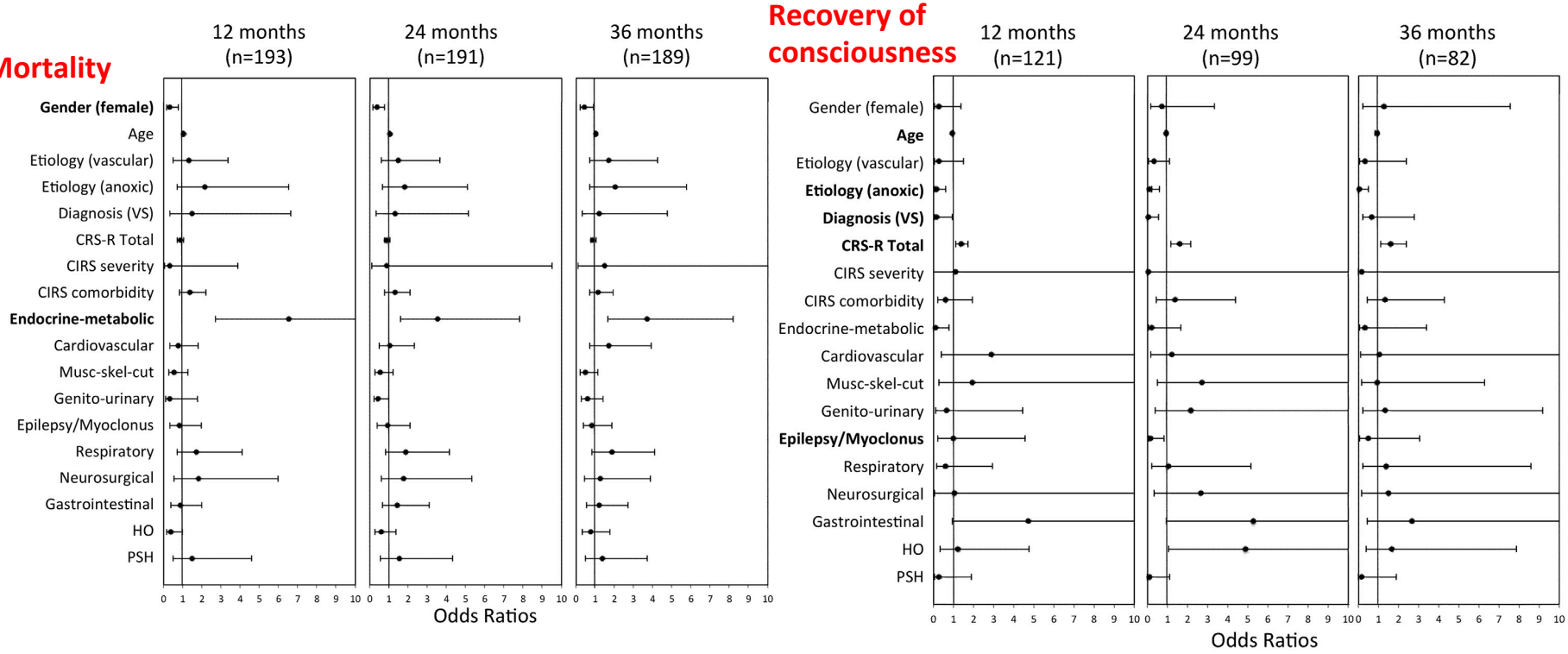
ACRM
Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2018;

ORIGINAL RESEARCH

Do Medical Complications Impact Long-Term Outcomes in Prolonged Disorders of Consciousness?

Anna Estraneo, MD,[a] Vincenzo Loreto, MD,[a] Orsola Masotta, Psy,[a] Angelo Pascarella, MD,[a] Luigi Trojano, MD[a,b]

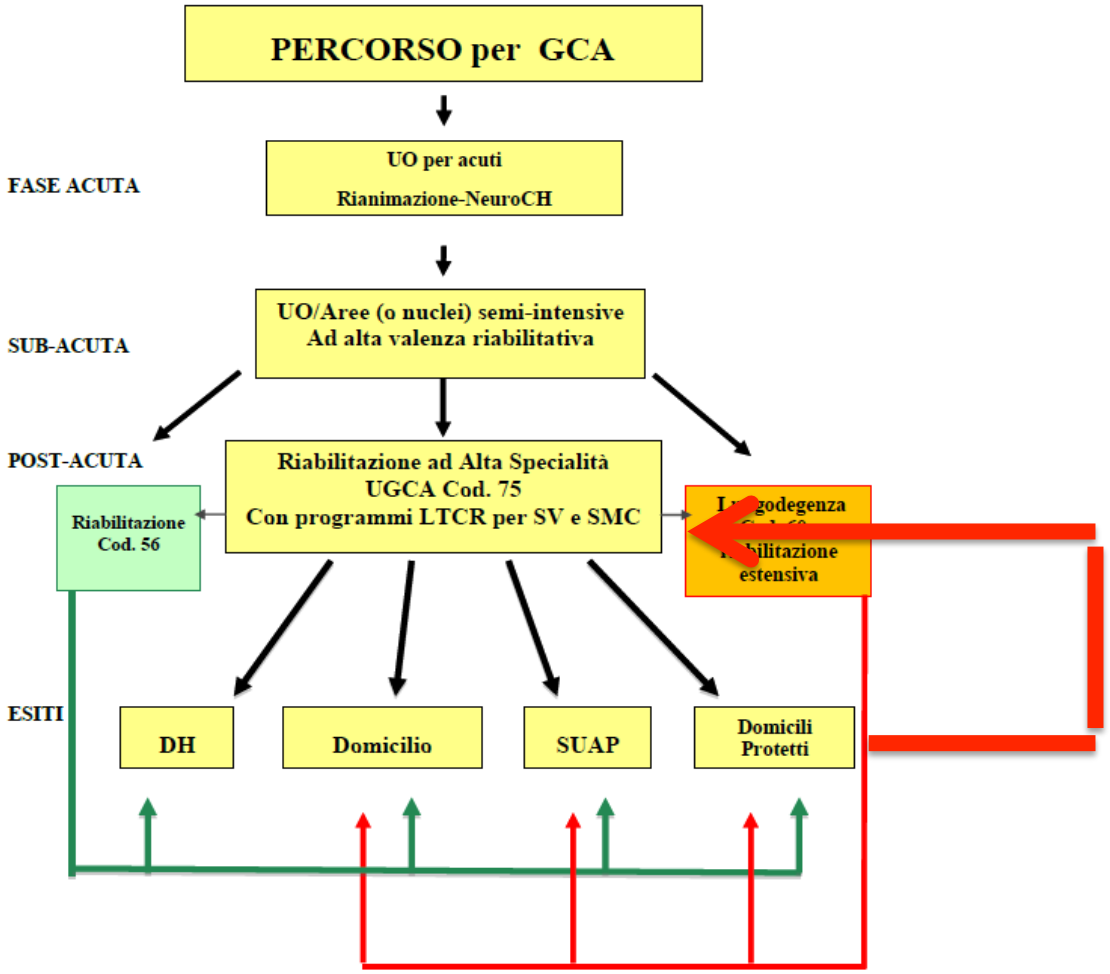
DoC=194 (VS= 142; MCS= 52)



Deciding the appropriate course of treatment in chronic DoC

Establishing:

- Appropriateness of different care pathways (MCS vs VS)
- Appropriateness of long-term rehabilitation treatment
- Appropriateness of chronic therapeutic management which guarantees for the patient (and their family) the maximum possible physical and mental well-being

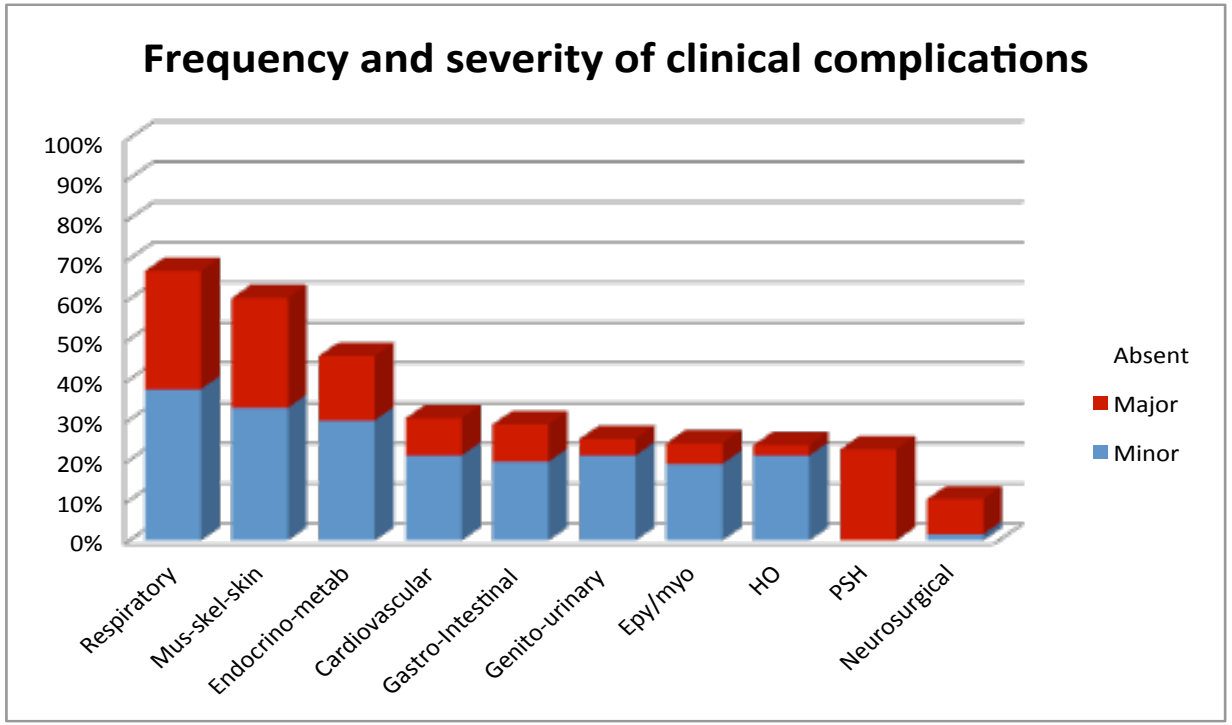


DdC: Criterio di congruenza diagnostica

BOZZA DM. CRITERI DI APPROPRIATEZZA DELL'ACCESSO AI RICOVERI DI RIABILITAZIONE OSPEDALIERA

Clinical complexity in chronic DoC

At least 1 CC in 188/194 patients (96.9%)



Estraneo et al., APMR, 2018

Clinical features in “late recovery” DoC at 25 and 60 mos

All late recovered patients had **severe functional disability:**

- marked spastic quadriparesis, with multiple joint limitations
- no patient recovered assisted standing
- no patient was autonomous in daily life activities and in transfers
- moderately severe disability (DRS= 8-10) in conscious patients, and extremely severe disability in MCS patients (DRS= 20-21)

Estraneo et al., APMR. 2014

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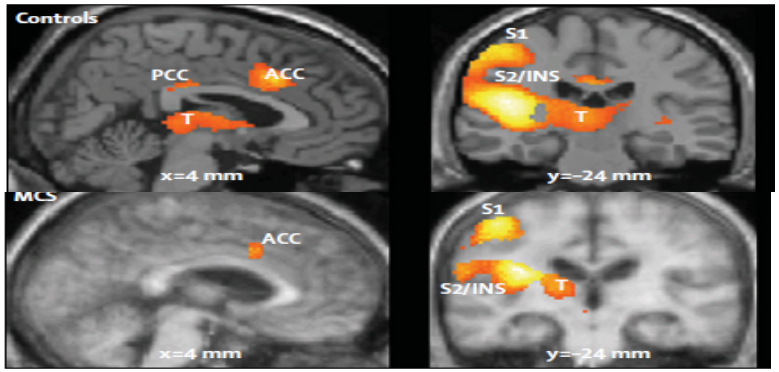
SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

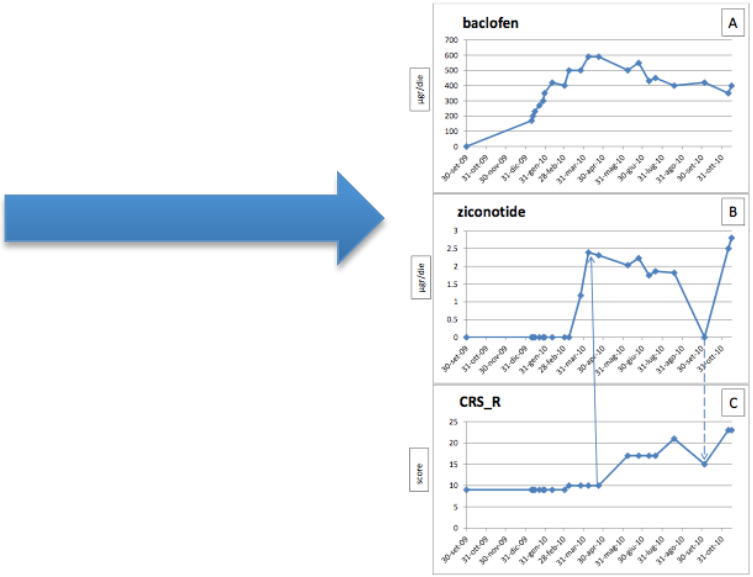
Practice guideline update recommendations summary: Disorders of consciousness

RECOMMENDED

13	Clinicians should assess individuals with a DoC for evidence of pain or suffering and should treat when there is reasonable cause to suspect that the patient is experiencing pain (Level B), regardless of level of consciousness. Clinicians should counsel families that there is uncertainty regarding the degree of pain and suffering that may be experienced by patients with a DoC (Level B).



Boly et al., 2008



Lanzillo et. al., EJPRM, 2014

"**Pain management and neuropalliative care** in chronic DoC. Nonetheless we advocate establishing a lower threshold for pain and symptom management because these patients are at risk for the under-treatment of pain." *(Fins JJ and Bernat JL, AMPR, 2018)*

Some considerations (1)

Controversies on appropriate treatment

- Conflict between patients' surrogate decision makers and physicians about the need of certain medical interventions (empirical data might show that some treatments are futile as the desired outcome is improbable)
- Conflict between individual patients' interests and interests of the community (related to limited health care resources)
- Conflict between scientific evidence of pain perception and ethical need to treat pain

Some considerations (2)

Ethical challenges about treatment

The chronic DoC cannot be considered “end of life” condition.

Clinicians should

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

- help families and surrogates to comprehend patients’ condition and prognosis in term of probability, and should propose treatment options respecting physical and moral well-being of patients and their families

Some considerations (3)

Ethical challenges about diagnosis and prognosis

The diagnosis and prognosis of (chronic) DoC show a critical level of uncertainty

Clinicians should take into account that:

- Recent scientific evidence stimulated novel complex controversies and questions about definition of (un)consciousness and prognosis

- At the moment new experimental data seem not to be readily applicable in clinical practice for all patients and enough reliable to solve medical and ethical issues

- Additional prognostic refinement for clarifying which VS might make late improvements are necessary

Some considerations (4)

Limitations and ethical challenges posed by new diagnostic technologies

Ideally, detection of (covert) brain activity might influence decision making by surrogates and clinicians

But:

- Only a selected sample of patients can be assessed;
- Study paradigms and methods of analysis are complex;
- Costs are high.

Because of these restrictions:

- No conclusive data about their reliability and feasibility
- Some of them remain investigational
- No application in routine care (not for all)

Towards an international consensus

SPECIAL ARTICLE

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Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research

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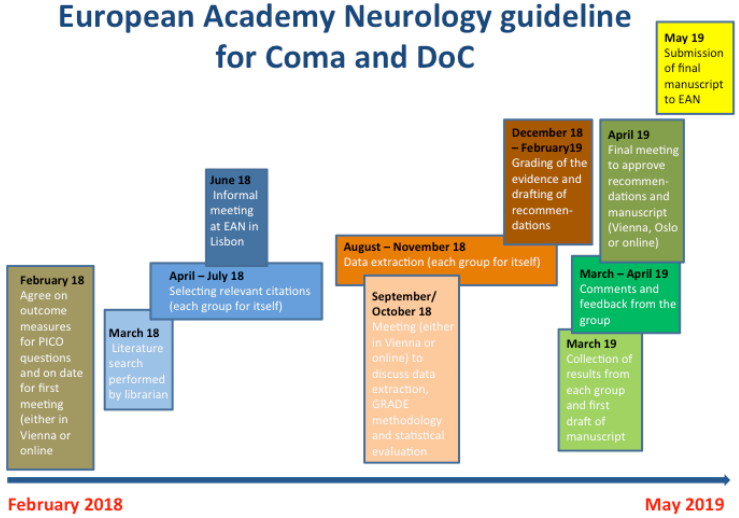
Neurology® 2018;00:1-11. doi:10.1212/WNL.0000000000005926

European Academy Neurology guideline for Coma and DoC



Italian guidelines on anoxic DoC

S.I.R.N.

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SOCIETÀ ITALIANA DI MEDICINA FISICA E RIABILITATIVA
The Italian Society of Physical and Rehabilitation Medicine

Federazione Nazionale Associazioni Trauma Cranico

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