Disorders of Consciousness: *optimizing patient care through translation of recent research developments into clinical practice*

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Summary

Background: Patients may survive after severe acquired brain injury with a Disorder of Consciousness (DOC) in the form of vegetative state (VS) or minimally conscious state (MCS). During recent years there has been a rapid expansion of knowledge of the neural substrates underlying these conditions, and new evidence that prognosis is not always as bad as previously thought. However clinical care remains variable. There are no guidelines on the rehabilitation management of these patients in Sweden, and a lack of consensus regarding what constitutes best practice. A review of how the evidence can best be applied to current clinical practice would help ensure that resources are used to best effect.

Objectives: To attempt a synthesis of current understanding of mechanisms and treatments with recommendations in existing guidelines for care of patients with DOC, to suggest key components for any future guidelines that may be developed for Sweden.

Methods: 1. A non-systematic review of studies of underlying neural substrates and prognosis of DOC, by means of the introduction *2.* A systematic review of studies of treatments for DOC, limited to studies with at least 10 patients published in the last 5 years. Inclusion criteria and search strategies are described. *3.* A semi-systematic, pragmatic review of existing guidelines and care protocols.

Results: Substrates and Prognosis: Studies show the importance of connectivity between neural networks for consciousness. Differences are seen between activation patterns in VS and MCS patients, including of pain pathways, supporting the importance of differentiating between these conditions. Several studies have reported recovery from VS and MCS more than a year after injury. Treatments: One large, well designed randomized, controlled trial, provides evidence for the efficacy of Amantadine in speeding recovery from DOC after traumatic brain injury (TBI). Evidence for other specific treatments remains weak, and the need for research networks to allow sufficiently large studies is urgent. Guidelines: Ten guidelines and protocols were identified. Many of these, some from healthcare systems similar to Sweden, give robust standards regarding rehabilitation care of DOC patients.

Conclusions: The evidence supports structured assessment and follow-up of DOC patients for at least a period of several years, and for use of Amantadine in patients with DOC after TBI. The development of Swedish guidelines for the care of DOC patients would help ensure a basic standard of care for all, and would support developments in evidence based care.

Objectives:

1. To provide, via the introduction, an update on current understanding of vegetative state and minimally conscious state (pathophysiological mechanisms, anatomical substrates, prognosis).
2. To review the literature from the last 5 years providing evidence for treatment methods aimed at improving function for patients in vegetative and minimally conscious states.
3. To review internationally available guidelines and protocols for management from the last 5 years.
4. To attempt a synthesis of current understanding of mechanisms, treatment, and of existing guidelines, to suggest key components for any future guidelines that may be developed for Sweden.

Introduction

There is currently a lack of consensus in Sweden regarding admission to inpatient rehabilitation units for patients in a vegetative state[1] (VS), and no Swedish guidelines regarding the care of patients with Disorders of Consciousness (DOC, i.e. VS and minimally conscious state [MCS]). Medical considerations collide with ethical and resource issues, and the level of follow-up (if any) offered to an individual patient can vary widely (*see appendix A for clinical context)*. The yearly reports from the Swedish national rehabilitation quality register (www.ucr.uu.se/webrehab/) actually show a fall in the number of patients with DOC admitted to inpatient rehabilitation units between 2008 and 2010.

Parallel to these difficulties, the scientific literature has seen a mushrooming of studies on the neural substrates underlying VS and MCS, new data on late recovery in some cases, and recent publication of a major treatment trial. It was therefore judged timely to perform a review of recent data on treatments options, and to consider how various health-care organizations have interpreted recent evidence in their formulation of guidelines for the care of patients with DOC, in those countries where they do exist.

Definitions and Terminology

The term "vegetative state" (VS) was introduced[2] to describe brain damaged patients who have spontaneous eye opening and sleep-wake cycles, but show no behavioural evidence of awareness of self or environment. In the 1990s "Minimally Responsive State[3]" was described, and in 2002, Giacino[4] gave a more robust definition for "Minimally Conscious State" (MCS),

which is still used today. MCS describes patients who show "clearly discernible" but inconsistent signs of consciousness, for example sustained visual tracking, localization of painful stimuli, and/or attempts at communication, without these reaching a functional level. Emergence from MCS is marked by the emergence of functional communication and/or functional object use.

Recently, subdivision of MCS into "MCS minus" and "MCS plus" has been proposed[5]. Patients in MCS showing lower level non-reflexive behaviours such as visual tracking are classified as "MCS minus", whilst those showing more complex behaviours such as command following (but not reaching criteria for emergence from MCS) classified as "MCS plus". Terminology for VS has also evolved; a new term "unresponsive wakefulness syndrome" has recently been proposed[6] to replace (and with the same definition as) VS, in part to avoid the derogatory connotations of the term "vegetative". Recent research using fMRI[7] and event related high density EEG[8] has showed preserved communicative ability in a very small minority of patients who seem to be in VS when assessed with behavioural methods. The term "functional locked-in syndrome" has been proposed to describe these patients[5]. A different terminology is used in central and eastern Europe[9]: "Apallic syndrome , Full Stage", and "Apallic Syndrome, Remission stage", these being similar but not identical concepts to VS and MCS.

The lack of ICD-10 codes for VS and MCS is also a barrier to developments in clinical practice and research. The draft version of ICD-11[10] does include such codes, which would represent progress.

*Brief comments on **diagnosis** of VS and MCS*

Before assessment for a possible DOC[14], the patient's general condition should be optimized, with attention to medication, environment, activity level and medical complications. Differentiating between VS and MCS is not easy, with erroneous clinical diagnosis of VS of up to 40% of patients[11], compared to diagnosis using standardized, behaviourally based assessment measures (e.g. Coma Recovery Scale Revised[12] [CRS-R]), which should therefore be used. Misdiagnosis must be avoided, as important differences exist between VS and MCS regarding brain functioning (neuroimaging evidence of activation of complex networks in MCS which is generally not present in VS), activation of higher pain pathways[13] (activation patterns similar to normals in MCS but not in VS) and prognosis (much better in

MCS). Some preliminary evidence[15] suggests that extending the total time for assessment, and possibly the use another standardized method[16] ("SMART") increases detection of higher level behaviours.

Imaging and Neurophysiology in Diagnosis of VS and MCS in clinical practice

Structural imaging is necessary to map the extent of brain injury and exclude treatable complications (e.g. hydrocephalus). EEG can similarly contribute to the understanding of severity and extent of injury, and exclude treatable factors, for example subclinical seizures. Evoked potentials add information on sensory pathways, and have prognostic value[17]. Studies have used fMRI[7] or high density EEG[8] to reveal awareness in a minority of patients who seem to be vegetative. However these methods are also known to give false negatives (i.e. some patients who at the bedside have clearly emerged from MCS will appear to be unaware on fMRI and EEG). Behavioural assessment thus remains the cornerstone of diagnosis.

Underlying pathophysiologcial and anatomical substrates of VS and MCS

For a person to be conscious, they must both have sufficiently high ***arousal*** (i.e. not be asleep or anaesthetized) and have ***awareness***. Laureys and colleagues[18] have highlighted that awareness has both ***internal*** (own thoughts, unrelated to external stimuli) and ***external*** (awareness of environment via sensory processing) components. fMRI studies[19] support the hypothesis that ***external awareness*** is subserved by a lateral frontoparietal network, of prefrontal and posterior parietal associative cortices, whilst ***internal awareness*** is enabled by connectivity in a medial frontoparietal network, encompassing the anterior cingulate/mesiofrontal cortex and posterior cingulate/precuneus. The recent development of methods for automatic classification of patients as being in VS or Locked-in, based on FDG-PET data reflecting activation in this internal awareness network, shows some early promise[20], although is not as yet useful at the individual patient level. Techniques for assessing *structural* integrity in white matter tracts using Diffusion Tensor Imaging (DTI) have also shown promise in differentiating VS from MCS, again at group level[21].

The important role of the thalamus in mediating cortical connectivity was illustrated by the successful use of thalamic deep brain stimulation in one patient who had been in MCS for 6 years[22]. However, 5 years later, there have been no well designed clinical trials of Deep Brain Stimulation. An interesting model[23] of recovery of consciousness after severe brain injury

incorporates evidence on the disruption of functional circuits in DOC, with knowledge of neurotransmitter pathways, to explain the effect of certain drugs on restoration of consciousness in some patients. Dopaminergic agents facilitate the output of medium spiny neurons of the striatum, which inhibit the Globus Pallidus interna (GPi), which itself inhibits the central thalamus. The end result of treatment with dopaminergic agents would thus be predicted to be increased thalamic activity with increased thalamocortical transmission. This model also explains the paradoxical effect of Zolpidem (a sleeping tablet) in *improving* responsiveness in some DOC patients. Zolpidem directly inhibits the GPi, thus decreasing GPi-mediated inhibition of the thalamus, and thus increasing responsiveness.

Prognosis

Previously it was considered that there was no chance of recovery from VS after 1 year for patients with traumatic brain injuries, or after 3 months for patients with non-traumatic injuries[24]. There was therefore no apparent motivation for longer term follow up. However these studies pre-dated the definition of MCS, prognosis of which has been uncertain, and also predated the development of standardized behavioural assessment tools, now known to improve diagnostic accuracy.

Several recent studies have shown that in fact a minority of patients do recover consciousness later after injury, and that the prognosis of MCS patients is clearly different to that of VS patients. Luauté *et al*[25] found that a third of MCS patients emerged from MCS later than a year after injury. Estraneo *et al*[26] found that 12/50 patients admitted to a specialist in-patient program for patients with VS>6 months emerged from VS during follow up, 10 of them more than a year after injury. These 10 "late recoverers" included 3 patients with non-traumatic injury. Katz *et al*[27] followed 36 patients with VS and MCS (trauma and non-trauma causes) from the time of admission to a specialist "slow-to-recover" rehabilitation program, for up to 4 years. The majority of patients emerged from MCS at latest follow up, nearly half of those followed for at least a year became independent at home, and a fifth returned to work or school.

Methods:

Methods for Objective 2: "A systematic review of treatment methods for VS and MCS":
Articles were identified as follows: *Search terms* "Vegetative state treatment" and "minimally conscious state treatment". *Search Engine:* PubMed. *Limits:* published in the last 5 years,

humans, adults, English, Swedish. *Type of article:* Original research manuscripts published in peer-reviewed journals. *Type of study*: Systematic reviews, Randomized controlled trials, Cohort studies, Case-control studies, Case series. *Number of patients:* n>=10. *Case definition*: VS or MCS according to recognized criteria. *Study objective:* study assesses influence of a specified treatment for VS or MCS on functional outcome or awareness. *Outcome measures:* Conscious level, functional level or communicative ability. *Additional exclusions:* studies on treatment methods focusing on the acute cause of brain injury and on measures to prevent VS or MCS. Quality of evidence was assessed, and recommendations for clinical practice made, using the SIGN system as a framework (http://www.sign.ac.uk).

Methods for Objective 3: "To review available guidelines and protocols for management of these patients": A semi-systematic, pragmatic search for relevant guidelines and care protocols available in the peer reviewed literature or on the world wide web.
Inclusion criteria for documents (all of the following): 1. Document issued by one of the following: national or regional organization, for example a government authority or health authority *Or* cited in PubMed. 2. Language: English or Swedish. 3. Document's focus: "Guideline", "Care Protocol", or other title with contents encompassing these concepts 4. Published in the last 5 years, 5. Gives recommendations for the care of patients in VS and/or MCS encompassing one or more of structure of care, admission to rehabilitation, duration of rehabilitation, assessment/diagnosis, treatment, follow-up, training.
Search strategies, Objective 3: 1. PubMed searches with key words "vegetative state", "minimally conscious state", "rehabilitation guideline", "care pathway" (limits humans, adults, published in last 5 years, English, Swedish) 2. Due to the low number of hits with strategy 1, the search strategy was extended to Google with search terms "acquired brain injury vegetative state guideline" with 21700 results (12/4 12) – the first 10 pages of results were screened. 3. Review of the author's archive.
Analysis of guidelines: Three standardized checklists were used to assess the nature of each documents, and the components of the recommendations (*tables x, y and z, Appendix C).*

Results

Objective 2: Treatment – advances in the last 5 years

The initial search yielded 212 articles. Abstracts of these articles were screened and the full text of the 8 of the 9 studies that appeared to meet the inclusion criteria was reviewed; the full text of one prospective study of a multimodal early-onset stimulation and rehabilitation

therapy[28] could not be accessed and this study was therefore excluded. A study of music therapy[29] focused on an assessment tool and did not evaluate any treatment effect, so was excluded. Another study[30] was primarily an evaluation of a behavioural assessment scale, without evaluation of any treatment. The remaining six articles met the inclusion criteria and are summarized in table A. One systematic review[31] that was identified during other searches did not include any additional studies that met the inclusion criteria, and is therefore not considered further.

Findings – objective 2:

1. There is *level 1+ evidence (SIGN system)* from one large, well performed, multicentre RCT[32], that *Amantadine* improves the rate of recovery of patients with VS or MCS after traumatic brain injury, in the setting of a rehabilitation program. *This supports a Grade B recommendation for this use of Amantadine.*
2. There is *level 2 evidence,* from one meta-analysis of 22 single-case studies[33] (one centre), that *Methylphenidate* has no effect on responsiveness of patients with VS or MCS. *This supports a Grade C recommendation that Methylphenidate not be used.*
3. There is *level 3 evidence* from one within-subjects retrospective case series[34] that a *structured, complex, multimodal rehabilitation intervention* over 12 weeks improved rates of emergence from VS and MCS. *This supports a Grade D recommendation on the use of structured multimodal rehabilitation programmes.*
4. There is *level 1- evidence* from one single-blind, pilot RCT[35], that intravenous administration of *branched-chain amino acids* increased the number of patients exiting VS. *The study authors recommend further research before any clinical recommendation.*
5. There is *level 3 evidence* from one uncontrolled case series[36] that *Deep Brain Stimulation* improved rates of emergence from VS. *Recommend further research before any clinical recommendation.*
6. There is *level 2+ evidence* from one placebo controlled crossover study[37] that *Zolpidem* improves responsiveness in a small minority of patients. *This supports a Grade C recommendation for trials of Zolpidem to improve responsiveness in DOC patients.*

One of the inclusion criteria for this study was a sample size of at least 10 patients. Studies with fewer patients can be useful as "proof of principle" or as hypothesis yielding studies, but they are very unlikely to give sufficient evidence to motivate a change in routine clinical practice. Of note, in the last 5 years, an additional 23 studies were published, with n<10, that

Table A: New evidence (last 5 years) on treatments for VS and MCS - studies with at least 10 patients

Ref	1st Author	Title	Year	Country	n	Aetiology	Time from injury to study start	Treatment under investigation	Study Design	Blinding	Basis for diagnosis of VS/MCS	Outcome measures	Findings - effect of intervention	Methodological quality of study (http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html)
39	Whyte	Incidence of Clinically Significant Responses to Zolpidem Among Patients with DOC	2009	USA	15	Trauma and non-trauma	1 month to 23 years, median 30,5 months	Zolpidem	Placebo controlled crossover study	Double blind	DRS>11, CRS-R, record review	Change in CRS-R score	Response in 1 of 15 patients	2+
36	DeFina	Improving outcomes of severe disorders of consciousness	2010	USA	41	Trauma and non-trauma	1 - >12 months	Advanced Care Protocol -12 weeks (daily therapy, drugs, median nerve stimulation, nutraceuticals)	within subjects retrospective case series, compared to historical controls	None	Clinical diagnosis - Mohonk report definition (2006)	DRS, CRS-R, FIM, GCS, clinical diagnosis	Significantly increased rates of clinical improvement	3
37	Aquilani	Branched-Chain Amino Acids May Improve Recovery From a Vegetative or Minimally Conscious State in Patients with Traumatic Brain Injury: A Pilot Study	2008	Italy	41	Trauma	0,6 - 3 months	Intravenous branched-chain amino acid infusions	Randomised, placebo controlled trial	Single blind (evaluating physicians blinded)	DRS>21	DRS	Greater improvement on DRS in intervention group, also greater number exiting VS or MCS	1-
35	Martin	The Effects of Methylphenidate on Command Following and Yes/No Communication in Persons with Severe Disorders of Consciousness	2007	USA	22	Trauma and non-trauma	3-100+ months	Methylphenidate	Retrospective meta-analysis of single-subject crossover studies	Single blind (data collectors blinded)	Clinical diagnosis by experienced team	Responsiveness and Accuracy - robust definitions given	No or negative effect of intervention on both outcome measures	2+
34	Giacino	Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury	2012	USA, Denmark, Norway	184	Non-penetrating Trauma	1-4 months	Amantadine	Multi-centre Randomised controlled trial	Double blind	DRS>11, and VS/MCS according to CRS-R	DRS	Faster improvement in treatment group	1+
38	Yamamoto	Deep brain stimulation for the treatment of vegetative state	2010	Japan	107 (21)	Trauma and non-trauma	4-8 months	Deep Brain Stimulation, applied for a minimum of 10 years	Non-randomised case series – 21 patients selected for treatment according to authors own neurophysiological criteria	None	Multi-Society Task Force criteria (1994)	Emergence from VS (method of assessment not specified)	Recovery in 8/21 treated patients and 0/86 untreated patients	3

DRS=Disability Rating Scale, FIM=Functional Independence Measure, CRS-R= Coma Recovery Scale Revised, GCS=Glasgow Coma Scale

otherwise met the inclusion criteria for this review. This highlights the need for the establishment of research networks in order to give sufficient power to future studies.

Objective 3: existing guidelines and care protocols:

The initial PubMed searches together yielded 6 articles, none of which in fact provided guidelines or care protocols regarding structure and extent of any rehabilitation. However a number of relevant articles were identified with broader searches with terms "vegetative state follow up" (261 hits) and "Disorders of Consciousness rehabilitation" (380 hits). A fully systematic review of all abstracts was not possible within the time constraints of this project. Instead, a rapid screening of titles was performed, leading to identification of five articles, encompassing one guideline, two evaluations of care protocols, and two evaluations of continuous care pathways for patients with traumatic brain injury. Additionally, with "google" searches on the internet four national or regional guidelines were identified and accessed as well as one expert report to a national government. The scope and origins of each of these sources (total n=10) are summarized (with alphabetic identifiers) in Appendix C, table x, and the components of the guidelines related to care pathways are summarized in Appendix C, table y. Additionally, personal communication with a Dutch physician[1] with an interest in this patient group yielded brief information about care pathways in Holland. The guidelines and protocols identified varied considerably in focus and on the degree of detail and specificity of recommendations. In addition to care pathways, other areas addressed included assessment and diagnosis (guidelines A,B,C,E,F,K [*see table x]),* treatment (both in terms of optimizing the patient's general condition to promote consciousness [A,C,K], and treatments (both drug and non-drug) targeted directly at increasing responsiveness [A, F, J, L], ethics [C], training of medical staff [F], and responsibility for ensuring implementation of the guideline [B]. Two *national government directives* were also identified during searches: A 2002 French directive on the creation of care units dedicated to people in chronic VS or MCS, recommending 6-8 bed units for each population area of around 300000 (http://www.sante.gouv.fr/fichiers/bo/2002/02-20/a0202031.htm), and very brief information in English on an Italian government directive http://www.west-info.eu/files/C_17_newsAree_1506_listaFile_itemName_0_file.pdf Translation of these documents would be of interest.

[*] Dr Van Erp, PhD student on patients in a vegetative state –supervisor Dr Jan Lavrijsen, elderly care physician/ nursing home physician and senior researcher, Radboud University Medical Centre.

Discussion

The original question was: "What constitutes optimal care for patients with DOC after acquired brain injury?" The above review of developments in understanding of pathophysiology and treatments of DOC, together with a review of existing international guidelines, begins to give some answers. One objective was consideration of treatments for VS/MCS. An area of difficulty was the definition of a "treatment". Specific drugs and interventions such as deep brain stimulation are clearly "treatments", with the aim of improving the patient's responsiveness. However, complex interventions such as rehabilitation programs have the same aim, could also be considered "treatments", and guidelines are one way of ensuring that such complex interventions are accessible to individual patients. Additionally, treatment trials of specific interventions have mostly been performed on a background of specialist care and a multidisciplinary neurorehabilitation programme. The results sections on treatments and on "guidelines and care protocols" should therefore be considered together.

There is a growing consensus[4,14] that the general condition of these patients must be optimized before an assessment for a possible DOC can be made. In such severely disabled patients this is in itself complex. Examples include (guideline A, http://www.gmpublichealthpracticeunit.nhs.uk/wp-content/uploads/2010/04/Low-Awareness-Care-Pathway-Report-Oct-2010.pdf): optimization of any intercurrent medical conditions, withdrawal or reduction of sedating medication, optimization of pain management, attention to nutritional status, bladder and bowel management, reduction of fatigue, optimal spasticity management and positioning (special seating), identification of any physical ability that could be used in communication. Environmental control is also considered important, and should include sensory regulation (avoid cognitive overload or deprivation), daily structure, and consistency during any assessment period.

To achieve all the above elements requires time (weeks rather than days) and a team with experience of the patient group. A survey of Swedish doctors[30] revealed that none of the responding rehabilitation physicians, and only 5% of responding neurologists had cared for more than 10 patients in VS during the previous 2 years. Such low exposure limits accumulation of the necessary experience, and this problem also applies to other members of the rehabilitation team (e.g. physiotherapists, occupational therapists).

Centralisation of care to one or two centres would be one possible solution, although has disadvantages in Sweden due to the very large distances involved, making contact with

relatives and information to social services difficult. Other models are possible, for example one or two "expert resource centres" that would work with local services on a consultative basis, possibly after a time-limited assessment period at a central facility, together with national guidelines to ensure a basic level of care for all patients.

Key findings from this essay to take forward to possible development of Swedish guidelines include:

1. Differentiation between VS and MCS is not easy and has not yet been answered by technological methods. Expert clinical diagnosis is needed, requiring use of standardized behavioural scales on several occasions. This will require both staff training and an appropriate care environment for the patient.
2. Differentiation between VS and MCS does matter, both from an ethical perspective, and because of important differences in prognosis.
3. Optimization of the patient's general condition is a prerequisite to an adequate diagnostic process, and requires that the patient is cared for in an appropriate environment by a team with experience of DOC.
4. Discharge planning for these patients is complex, and existing linear concepts whereby medical care ends (the patient must have "completed treatment") before social services become involved in discharge planning, are not appropriate for this patient group. An overlap period of up to several months may be needed.
5. Late recovery from both VS and MCS does occur in a minority of patients. This may not be apparent to carers. A structured follow-up is therefore needed to allow appropriate active rehabilitation interventions as and when they become appropriate, and to address ethical issues.
6. Treatment with Amantadine improves rate of recovery from DOC for patients with traumatic brain injuries, and should be offered as long as no contraindication exists (*Grade B recommendation)*. In Sweden this requires application for a special licence as Amantadine is not registered with the Medical Products Agency, and a national policy regarding this would ensure that all appropriate patients received Amantadine in a safe manner, and reduce the amount of work required to apply for licences.
7. Treatment with Zolpidem is effective in the small minority of patients who are "responders". If tested, a structured evaluation of effect should be performed, with standardized scales, together with a replication procedure if an effect is seen. *Grade C recommendation.*

8. Evidence for other specific treatments is not currently strong enough to allow their recommendation in clinical practice, although several areas seem promising (e.g. deep brain stimulation). Development of a research network is suggested to allow participation in future research into such treatments.
9. Several well formulated guidelines regarding care for these patients exist in other countries. Some of these guidelines refer to healthcare systems and cultures not dissimilar to Sweden (e.g. England, Scotland, Australia), and it would be appropriate for a potential future "guideline-formulation group" in Sweden to review these.

Other treatment methods of interest

Other methods of neuromodulation have shown promise (in single case studies and in case series too small for inclusion in this essay), although the evidence base is not yet strong enough to recommend their use in clinical practice. Transcranial magnetic stimulation, direct current stimulation, and median nerve stimulation are all methods of interest. Even intrathecal baclofen (with a primary aim of improving responsiveness rather than treating any spasticity) has been studied. The challenge to the research community is now to produce sufficiently robust studies to support or refute the introduction of these methods in health care.

Resource issues: It is possible that formal protocols and dedicated units for VS/MCS care actually lead to reduced costs to society, and health-economic analyses of different health and social care models for this patient group would be of interest.

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