

# The Vegetative and Minimally Conscious States: Diagnosis, Prognosis and Treatment

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## KEYWORDS

- Consciousness • Vegetative state • Traumatic brain injury
- Neuroimaging • Outcomes

Severe acquired brain injury has profound impact on alertness, cognition, and behavior. Among those who survive the initial injury, a significant minority fail to fully recover self and environmental awareness, and go on to experience prolonged disorders of consciousness (DOC) that can last a lifetime. Following emergence from coma, most individuals evolve into either a vegetative (VS) or minimally conscious state (MCS). Prevalence rates are difficult to estimate in the United States because of the lack of systematic surveillance procedures and range from 25,000 to 420,000<sup>1,2</sup> for VS and 112,000 to 280,000<sup>3</sup> for MCS. Patients, families, providers, and caregivers are all affected by the personal, financial, and societal consequences of prolonged VS and MCS. Although there are no standards of care to guide clinical management, a growing body of empirical evidence is beginning to accrue to inform clinical decision making. In this article, we review the state of the science as it pertains to diagnosis, prognosis, and treatment of patients with DOC.

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The authors have nothing to disclose.

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Neurol Clin 29 (2011) 773–786

doi:[10.1016/j.ncl.2011.07.009](https://doi.org/10.1016/j.ncl.2011.07.009)

[neurologic.theclinics.com](http://neurologic.theclinics.com)

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## HISTORICAL CONTEXT

In the 1890s, William James<sup>4</sup> construed consciousness as “awareness of the self and the environment.” He viewed conscious awareness as the product of sensory and subjective experiences. For James, the “objects of our consciousness” included the environment and one’s mental state. The evidence for consciousness was provided by “reactions” elicited by either internal or external events.<sup>4</sup> Three-quarters of a century later, Jennett and Plum<sup>5</sup> parsed arousal from awareness in considering consciousness, and proposed the term, “persistent vegetative state (PVS)” to refer to a state of “wakefulness without awareness.” More than 2 decades after PVS was defined, the Multi-Society Task Force Report on PVS clarified that whereas “awareness requires wakefulness, wakefulness can be present without awareness.”<sup>1</sup> The Task Force definition highlighted the preservation of sleep-wake cycles and concluded that PVS represents a wakeful state in which there is complete inability to experience the environment.<sup>1</sup>

In 1995, shortly after the release of the Multi-Society Task Force on PVS, the Aspen Neurobehavioral Workgroup was convened to reconcile disparities between diagnostic and prognostic recommendations proposed by the Task Force, and a position statement published a year later by the American Congress of Rehabilitation Medicine (ACRM).<sup>6</sup> The Aspen Workgroup included representatives from neurology, neurosurgery, neuropsychology, physical medicine and rehabilitation, nursing, allied health, and bioethics. After achieving consensus on the diagnostic and prognostic guidelines for VS, the Workgroup shifted its attention to the subpopulation of patients who showed minimal or inconsistent behavioral signs of consciousness. The term, “minimally responsive state (MRS)” had previously been proposed by the ACRM to differentiate patients who retained some definitive, albeit inconsistent, signs of conscious awareness from those in coma and VS.<sup>6</sup> The ACRM recommended to apply the term “MRS” when an “unequivocally meaningful” behavioral response was observed following a specific command, question, or environmental prompt on at least one occasion during a period of formal assessment. The Aspen Workgroup subsequently recommended to replace the term “MRS” by “MCS” to emphasize the partial preservation of consciousness that distinguishes this condition from coma and VS.<sup>7</sup>

## DIAGNOSTIC ASSESSMENT

### *Vegetative State*

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A primary aim in clinical management of patients with DOC is to establish an accurate diagnosis. Critical decisions concerning prognosis and treatment rest heavily on the accurate determination of level of consciousness. The Multi-Society Task Force Report was pivotal to clinical practice, as it established operationally defined diagnostic criteria for the first time, proposed prognostic guidelines for recovery of consciousness and function, and evaluated the effectiveness of specific treatment interventions. The report also introduced the notion that VS usually exists as a transitional state between coma and higher levels of consciousness, and clarified that VS is considered “persistent” when this state lasts at least 4 weeks. The Task Force also proposed temporal parameters for the “permanent vegetative state” to establish the point at which the probability of subsequent recovery of consciousness is very low.<sup>1</sup> Relying on available outcome studies from around the world, the Task Force concluded that VS should be considered permanent after 3 months following hypoxic-ischemic, metabolic, and congenital causes, but not until 12 months after traumatic brain injury.

The diagnostic criteria for PVS recommended by the Task Force were met with broad consensus internationally and remain in force today. All of the following behavioral criteria must be met on bedside examination to establish the diagnosis of VS<sup>1</sup>:

- Intermittent wakefulness manifested by the presence of sleep/wake cycles (ie, periodic eye opening)
- No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli
- No evidence of language comprehension or expression.

The development of behaviorally based criteria for detecting conscious awareness at the bedside has advanced research and clinical practice by constructing a common frame of reference from which to consider the boundary between consciousness and unconsciousness. Nonetheless, studies of diagnostic accuracy consistently suggest that 30% to 40% of patients unable to speak or follow commands are falsely diagnosed with VS.<sup>8-10</sup> Diagnostic error in DOC can have dramatic consequences given the influence of early diagnosis on decisions relating to continuation of life support, indications for neurorehabilitation, caretaker planning, and family adjustment.

### ***Minimally Conscious State***

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After completing a systematic review of the literature, the Aspen Workgroup defined MCS as “a condition of severely altered consciousness in which there is *minimal but definite* behavioral evidence of conscious awareness.” Behaviorally based diagnostic criteria were proposed and published in *Neurology* in 2002.<sup>7</sup> To establish the diagnosis of MCS, clearly discernible evidence of 1 or more of the following behaviors must be observed on bedside examination:

- Simple command-following
- Intelligible verbalization
- Recognizable verbal or gestural “yes/no” responses (without regard to accuracy)
- Movements or emotional responses that are triggered by relevant environmental stimuli and cannot be attributed to reflexive activity (eg, visual pursuit of a moving object).

The Aspen Workgroup recognized that as recovery of consciousness moves forward, an upper bound for MCS also needed to be established. Consequently, 2 behaviors were defined to mark “emergence from MCS” (EMCS): reliable demonstration of “interactive communication” (ie, accurate yes and no answers to situational orientation questions) and “functional object use” (ie, demonstration of 2 different familiar objects). Unlike the diagnosis of MCS, which requires evidence of *reproducible* goal-directed behavior, emergence from MCS requires *consistent* demonstration of volitional behavior.<sup>7</sup> **Table 1** lists the distinguishing behavioral features of coma, VS and MCS.

### ***Neurobehavioral Rating Scales***

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In an effort to minimize diagnostic and prognostic error associated with assessment of patients with DOC, standardized neurobehavioral rating scales have been developed. The Glasgow Coma Scale (GCS), originally published in 1974, continues to be the standard for acute assessment of patients with DOC.<sup>11</sup> The longevity of the GCS is attributable to its strong inter-rater reliability, ease of administration, and well-established relationship to mortality and morbidity. The limitations of the GCS have also been well documented.<sup>12</sup> Among these, lack of sensitivity to subtle changes of

<b>Behavior</b>	<b>Coma</b>	<b>Vegetative State</b>	<b>Minimally Conscious State</b>
Eye opening	None	Spontaneous	Spontaneous
Spontaneous movement	None	Reflexive/Patterned	Automatic/Object Manipulation
Response to pain	Posturing/None	Posturing/Withdrawal	Localization
Visual response	None	Startle/Pursuit (rare)	Object recognition/Pursuit
Affective response	None	Random	Contingent
Commands	None	None	Inconsistent
Verbalization	None	Random vocalization	Intelligible words
Communication	None	None	Unreliable

prognostic relevance has received the most attention. In response to this concern, a wide array of measures especially designed for long-term monitoring of patients with DOC have been developed.<sup>13,14</sup> Although many of these newer instruments offer a standardized approach to assessment, until recently, their psychometric underpinnings had not been empirically scrutinized.

In 2010, the Disorders of Consciousness Task Force of the ACRM completed an evidence-based review of behavioral assessment scales for patients with DOC.<sup>15</sup> Thirteen scales met the review criteria and were evaluated on their ability to differentiate VS, MCS, and EMCS; inter-rater reliability; diagnostic validity; and prognostic validity. The review concluded that among the scales reviewed, the Coma Recovery Scale—Revised (CRS-R)<sup>16</sup> received the most “acceptable” ratings in the categories investigated. The CRS-R is composed of 6 subscales addressing auditory, visual, motor, oromotor/verbal, communication, and arousal functions. Subscale items are hierarchically arranged with the lowest items reflecting brainstem-mediated functions and the highest items corresponding to cortical functions. CRS-R administration and scoring guidelines are manualized and the scale is intended for use by licensed medical and allied health professionals. The CRS-R was selected as the measure of choice for assessment of recovery of consciousness by the Interagency Traumatic Brain Injury Common Data Elements Outcomes Workgroup,<sup>17</sup> and has been used to investigate diagnostic accuracy,<sup>8,18</sup> the relationship between behavioral and neurophysiologic markers of consciousness,<sup>19–21</sup> outcome prediction,<sup>22,23</sup> and treatment effectiveness.<sup>24,25</sup> The scale is currently available in 12 languages (English, Spanish, Portuguese, Italian, French, Greek, German, Dutch, Norwegian, Danish, Swedish, Korean). **Fig. 1** shows the CRS-R Record Sheet.

### ***Neuroimaging Applications in Diagnostic Assessment***

The development of diagnostic applications of neuroimaging for patients with DOC has generated novel data that have begun to challenge conventional beliefs about the primacy of behavior in the assessment of level of consciousness. Detecting volitional behavior in patients with severe brain injury is often difficult, as fluctuations in arousal level, deficient drive, and sensory and motor impairments can mask signs of consciousness. Functional neuroimaging strategies provide a means of assessing cognition without reliance on verbal or motor behavior. Recent investigations have demonstrated the utility of functional neuroimaging paradigms designed to assess command-following ability in patients who lack the capacity for speech or active movement.<sup>26,27</sup>

<b>Coma Recovery Scale – Revised</b> ©2004 <b>Record Sheet</b>																
This form should only be used in conjunction with the CRS-R Administration and Scoring Manual which defines guidelines for standardized application of the scale																
<b>Patient:</b>					<b>Diagnosis:</b>					<b>Etiology:</b>						
<b>Date of onset:</b>					<b>Date of Examination:</b>											
<b>Date</b>																
<b>Week</b>																
<b>AUDITORY FUNCTIONS</b>																
4 Consistent Movement to Command *																
3 Reproducible Movement to Command *																
2 Localization to Sound																
1 Auditory Startle																
0 None																
<b>VISUAL FUNCTIONS</b>																
5 Object Recognition*																
4 Object Localization: Reaching*																
3 Visual Pursuit *																
2 Fixation*																
1 Visual Startle																
0 None																
<b>MOTOR FUNCTIONS</b>																
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																
<b>OROMOTOR/ VERBAL FUNCTIONS</b>																
3 Intelligible Verbalization*																
2 Vocalization / Oral Movement																
1 Oral Reflexive Movement																
0 None																
<b>COMMUNICATION SCALE</b>																
2 Functional: Accurate**																
1 Non-functional: Intentional*																
0 None																
<b>AROUSAL SCALE</b>																
3 Attention																
2 Eye opening without stimulation																
1 Eye opening with stimulation																
0 no arousal response																
<b>TOTAL SCORE</b>																
Denotes emergence from MCS**																
Denotes MCS*																

**Fig. 1.** Record Sheet for the Coma Recovery Scale—Revised (CRS-R) excerpted from the CRS-R Administration and Scoring Manual (available from the authors by request). (From Giacino JT, Kalmar K. CRS-R Administration and Scoring Manual. Johnson Rehabilitation Instituion; with permission. Copyright © 2004.)

In a typical functional magnetic resonance imaging (fMRI) paradigm, the patient is instructed to perform a basic cognitive task while in the scanner. Regions of brain activity observed during task performance are compared with areas that are active during passive sensory stimulation and during periods of rest. Task-specific activation profiles are first acquired in healthy volunteers to serve as a normal referent for patient studies. A growing body of fMRI studies indicates that some patients who fail to show any behavioral evidence of response to commands administered at the bedside, produce activation profiles that are nearly indistinguishable from healthy volunteers performing similar command-following tasks while in the scanner.<sup>26-28</sup>

Owen and colleagues<sup>26</sup> identified a patient diagnosed with VS 5 months after sustaining a traumatic brain injury who was able to perform 2 different mental imagery

tasks when instructed to do so during a series of fMRI scans. Selective activation was noted in the supplementary motor area in response to instructions to imagine playing tennis. In contrast, activation was noted in the parahippocampal gyrus and posterior parietal cortex when the patient was instructed to imagine walking around the rooms of her house. Although this patient was reportedly showing signs of visual fixation at the time of the study (suggesting transition from VS to MCS), this landmark study demonstrated the potential role of neuroimaging in detecting cognition in patients with underlying impairments unrelated to alterations in consciousness.

Rodriguez-Moreno and colleagues<sup>28</sup> developed a second fMRI-based command-following paradigm using a silent picture-naming task to capture internal speech in patients with varying degrees of impaired consciousness ranging from VS to the locked-in syndrome (LIS). In LIS, there is no speech and little to no active movement, although cognitive functions are well preserved. As expected, robust language network activation was observed in the patient with LIS, a patient who had emerged from MCS, and 2 patients in MCS. In addition, 1 patient in VS also evidenced widespread activation of the language network, including the superior temporal, inferior frontal, and medial frontal gyri. The investigators also found that patients with higher CRS-R scores showed more complete activation of language structures, suggesting that fMRI activation profiles may provide information concerning residual cognitive function that cannot be extracted at the bedside.

Monti and colleagues<sup>29</sup> developed passive listening and active auditory target detection tasks to evaluate executive functions in patients with no evidence of command-following on bedside testing. Healthy volunteers demonstrated activation of fronto-parietal networks in response to instructions to perform the target detection task. A similar activation pattern was observed in one patient in MCS suggesting compliance with the task demands.

An elegant follow-up study completed by Monti and colleagues<sup>30</sup> converted Owen and colleagues'<sup>26</sup> previously described imagery-based command-following paradigm into a yes-no signal system. Patients were instructed to imagine either playing tennis or walking around the rooms of their house when they wished to answer "yes," and to perform the opposite task when they wished to answer "no." Although 5 of the 54 patients (VS = 23; MCS = 31) were able to selectively trigger motor and spatial network activation on cue, 1 patient in MCS was able to use the imagery paradigms to reliably answer yes-no questions, despite the absence of this behavior on bedside examination.

These referenced studies indicate that at least some patients who appear unresponsive may retain higher levels of self and environmental awareness than would otherwise be suggested on bedside examination. As such, functional neuroimaging paradigms may eventually play an important role in reducing diagnostic error and improving prognostic accuracy.

## PROGNOSIS

Duration of unconsciousness appears to be one of the strongest discrete predictors of subsequent recovery of consciousness.<sup>1,31</sup> Among patients who remain in VS for 3 months following traumatic brain injury, approximately 35% will recover consciousness by 1 year after injury. In nontraumatic VS lasting 3 months, the probability of recovery of consciousness at 1 year is substantially lower, dropping to approximately 5%. After 6 months in traumatic VS, there is still a 15% probability of recovery of consciousness as compared with near zero in nontraumatic VS.<sup>1</sup>

Regarding prognosis in MCS, Giacino and Kalmar<sup>22</sup> monitored the course of recovery across the first year after injury on the Disability Rating Scale (DRS) in 104

patients (MCS = 55; VS = 49) admitted to an inpatient rehabilitation program. Fifty percent of the MCS group fell within the “no to moderate disability” category on the DRS at the 12-month mark as compared with only 3% of those in VS. When the 2 diagnostic groups were further stratified by etiology, 38% of patients in traumatic MCS versus only 2% of those in nontraumatic VS had “no to moderate disability” at 12 months.

Although large group studies have identified clinical variables tied to outcome, there is no prognostic algorithm with high sensitivity and specificity at the single-case level. This is, in part, because of the lack of systematic study of the influence of mediating variables, such as quality of care on outcome. The existing prognostic guidelines for VS developed by the Multi-Society Task Force are almost 2 decades old and guidelines do not yet exist for MCS. In view of these circumstances, an expert panel jointly sponsored by the American Academy of Neurology, American Congress of Rehabilitation Medicine, and National Institute on Disability and Rehabilitation Research has been convened to conduct an evidence-based review of the literature and provide recommendations for practice. This initiative is expected to be completed in 2013.

### **Late Recovery in VS and MCS**

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The Multi-Society Task Force guidelines on PVS provided the first evidence-based guideline for permanent VS.<sup>1</sup> However, there were relatively few reports in the literature at the time of the Task Force review that included patients followed beyond 12 months after injury. Consequently, the number of potential recoveries occurring beyond the recommended temporal cutoffs for permanence was truncated. In addition, most of the available studies relied on “pooled” data that failed to distinguish outcomes between patients in VS and MCS. To avoid the risk of incorrectly inferring permanence, the Aspen Workgroup recommended abandoning the term, “permanent VS.” Instead, the Workgroup recommended specifying the etiology (ie, traumatic or nontraumatic) and time since onset when diagnosing VS.<sup>7</sup>

Recent evidence suggests that the window for recovery of consciousness and function may extend well beyond 1 year in a substantial minority of patients.<sup>32–34</sup> Estraneo and colleagues<sup>33</sup> tracked recovery in 50 patients in traumatic and nontraumatic VS for an average of 26 months. The investigators reported that 20% of the sample recovered at least one sign of conscious awareness between 14 and 28 months after injury, and 24% emerged from MCS between 19 and 25 months after injury. Late recovery of consciousness was significantly associated with younger age at onset, traumatic etiology, and preserved pupillary response at the time of enrollment.

Lammi and colleagues<sup>32</sup> followed 18 patients who were in posttraumatic MCS at the time of discharge from inpatient rehabilitation for up to 5 years. Although outcomes were similar to those reported by Giacino and Kalmar<sup>22</sup> at 1 year after injury, more than one-third of the sample recovered to an independent level of cognitive or motor function between 2 and 5 years after injury. Interestingly, length of MCS was not significantly correlated with outcome on the DRS, suggesting that improvement to MCS may have been the critical variable in extending the recovery window.

Katz and colleagues<sup>31</sup> monitored outcomes in 36 patients who were admitted to a rehabilitation program at approximately 1 month following injury with a diagnosis of VS ( $n = 11$ ) or MCS ( $n = 25$ ). Seventy-two percent of the sample (VS = 5/11; MCS 20/25) emerged from MCS at an average of 9 weeks after injury, 58% (VS = 4/11; MCS = 17/25) recovered orientation at an average of 16 weeks after injury, and 28% (VS = 1/11; MCS = 9/25) regained household independence 33 weeks after injury on average. The investigators concluded that patients in VS who emerge

to MCS within the first 8 weeks after injury are more likely to progress to higher levels of functional independence over the course of the next 1 to 4 years. Those who remained in MCS were more likely to have sustained a nontraumatic brain injury and to have been in VS longer than 8 weeks. These results support prior reports, suggesting that outcome from MCS is considerably more heterogeneous relative to VS.

### ***Neuroimaging Applications in Prognosis***

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Neuroimaging studies may provide unique information to prognostic decision making in patients suspected or known to have neurologic impairments that confound bedside assessment. The so-called “default mode network (DMN)” has garnered attention in this regard given its structural and functional characteristics. Functional MRI studies have identified the DMN as a network of interconnected structures composed of the medial prefrontal cortex, temporo-parietal junction, and precuneus.<sup>35</sup> This circuit is believed to activate during periods of cognitive quiescence and deactivates in response to active cognitive processing. The DMN has been linked to conscious awareness in that it appears to have a role in scanning for salient environmental events and monitoring the interface between external events and the internal state.<sup>36</sup> Functional MRI studies indicate that the degree of DMN connectivity is greater in MCS relative to VS, and that severity of cognitive impairment appears to be proportional to the extent of the DMN connectivity.<sup>37</sup> Preserved DMN connectivity may be a harbinger of more favorable outcome.

In another series of fMRI studies, Coleman and colleagues<sup>19</sup> used a hierarchical language-processing paradigm to evaluate the integrity of the language network in 44 patients with DOC (VS:  $n = 22$ ; MCS:  $n = 19$ ). Subjects were exposed to linguistic material of variable semantic complexity to gauge the depth of processing. Activation profiles were categorized based on degree of impairment and outcomes compared across impairment categories. Results revealed a clear association between the integrity of the fMRI results and behavioral performance on the CRS-R at 6 months, suggesting a relationship between degree of language network activation and functional recovery.

Structural imaging studies may also play a role in informing prognosis in patients with DOC. Newcombe and colleagues<sup>38</sup> used diffusion tensor imaging (DTI) to evaluate the structural integrity of white matter pathways in a cohort of patients with traumatic ( $n = 7$ ) and nontraumatic ( $n = 5$ ) VS. The relationship between DTI abnormalities, language network fMRI activation profiles, and behavioral performance on the CRS-R was explored. DTI detected supratentorial white and gray matter changes in both groups that were not observed on conventional MRI sequences, and white matter abnormalities were more prevalent in the brainstem in patients with traumatic injuries. Correlation analyses indicated that patients with more extensive white matter abnormalities tended to perform more poorly on fMRI activation studies and received lower CRS-R scores. Early DTI may be useful in identifying characteristic lesion profiles associated with lower cognitive reserve and less favorable behavioral outcomes.

## **TREATMENT**

Treatment interventions for patients with DOC should incorporate both preventive and restorative strategies. Immediately after injury, patients in VS and MCS are at risk for multiple complications arising from immobility. Muscle, tendon, and soft tissue contractures; skin breakdown; thrombo-embolic disease; and pulmonary or urinary tract infections are among the most common foci for prevention efforts. Despite the absence of a sufficient body of evidence to support definitive practice guidelines, restoration of



sleep-wake cycles, nutritional balance, bowel and bladder regulation, and large joint passive mobilization should constitute basic clinical management aims.<sup>39</sup>

Restorative interventions are intended to promote arousal and drive goal-directed behavior. Centrally active medications, sensory stimulation, procedures, hyperbaric oxygen therapy, and deep brain stimulation have all been used to promote rate of recovery and reduce the severity of residual functional disability, although there is insufficient evidence to guide the selection of any particular intervention. In general, treatment-effectiveness studies have been compromised by small sample sizes, failure to mitigate examiner bias, and use of crude outcome measures.<sup>39,40</sup> In addition, caregivers are hesitant to provide consent for clinical trials that constrain the use of other potentially helpful medications.<sup>41</sup> Notwithstanding the limitations of the existing evidence base, clinicians are obligated to provide reasonable rehabilitative treatment options. In **Table 2** and in the following paragraphs, we briefly describe and review the results of some representative treatment studies.

Amantadine hydrochloride (AH) is commonly used in neurorehabilitation settings to enhance arousal and behavioral initiation in patients with DOC. A single-center randomized crossover trial conducted by Meythaler and colleagues<sup>42</sup> compared cognitive and motor changes in 35 patients with GCS scores of 10 or lower who received either AH or placebo for a period of 6 weeks. After the initial 6 weeks, patients were crossed to the alternate condition for an additional 6 weeks. Results suggested that patients treated with AH first showed faster gains on cognitive (ie, Mini Mental Status Examination) and functional status (ie, DRS) measures; however, there was no significant difference between the 2 groups when outcomes were reassessed at the 12-week mark. There was also evidence that the 2 groups were not equivalent with regard to injury severity.

Dramatic “awakenings” from states of unresponsiveness have been reported following administration of the soporific, zolpidem. The first case was described by Clauss and colleagues<sup>43</sup> in 2000 and additional case reports and case series have followed.<sup>44–48</sup> In the largest series reported to date, Whyte and Myers<sup>45</sup> monitored the response to zolpidem (10 mg) in 15 patients in traumatic and nontraumatic VS and MCS using a double-blind, placebo-controlled crossover design. Although only 1 of 15 subjects was considered a zolpidem “responder,” behavioral changes were significant in that the responsive patient transitioned from VS to MCS following administration of the drug, and this effect was replicated over repeated trials. The paradoxical effect of zolpidem has been hypothesized to be related to “relaxation” of tonic inhibitory influences stemming from pallidal outflow to the thalamocortical system caused by striatal dysfunction.<sup>49</sup>

More definitive evidence regarding the effectiveness of amantadine and zolpidem in facilitating recovery in patients with DOC is likely to emerge from 2 recently launched double-blind prospective randomized placebo-controlled multicenter clinical trials. The first, a recently completed 10-site international trial of AH funded by the National Institute on Disability and Rehabilitation Research (NIDRR) is designed to determine whether short-term functional outcome is more favorable in posttraumatic VS and MCS patients exposed to amantadine versus placebo within 4 to 16 weeks of injury. The trial will also determine whether functional gains are maintained after drug washout (NIDRR Award #H133A031713). The second trial, also NIDRR funded, aims to determine the rate and mechanism of effect of zolpidem among individuals remaining in traumatic or nontraumatic VS and MCS for at least 4 months (NIDRR Award #H133G080066).

Nonpharmacologic treatment efforts in this population have historically focused on the use of sensorimotor stimulation. This strategy is premised, in part, on the notion

**Table 2**  
**Representative studies illustrating treatment interventions for patients with disorders of consciousness**

<b>Intervention</b>	<b>Rationale</b>	<b>Method</b>	<b>Aim</b>	<b>Representative Study</b>	<b>Results</b>
Pharmacotherapy	Drug exposure may correct imbalance in inhibitory and facilitory neural systems responsive for symptom expression	Administration of dopaminergic, noradrenergic, and serotonergic medications	Improve arousal, initiation, and attention	Meythaler et al, <sup>42</sup> 2002	Rate of recovery significantly faster in patients treated with amantadine hydrochloride within 3 months of injury relative to placebo group.
Sensory stimulation	Information processing is dependent on calibration of stimulus intensity and response threshold	Administration of multimodal sensory stimuli (auditory, tactile, visual, olfactory)	Improve breadth and reliability of behavioral response repertoire	Mitchell et al, <sup>50</sup> 1990	Time to recovery of command-following and purposeful movement significantly shorter (mean difference = 5 days) in patients who received a structured sensory stimulation program for 1–2 hours/day over 7–12 days relative to no-treatment controls.
Deep Brain Stimulation (DBS)	Electro-physiologic stimulation of reticular-activating system produces physiologic changes associated with arousal	Chronic electrical stimulation of meso-diencephalic structures	Improved arousal and/or cognitive deficits associated with disruption of thalamo-cortical circuits	Schiff et al, <sup>25</sup> 2007	Improvement in arousal ratings, praxis, and swallowing on standardized assessments obtained during DBS-on vs off periods.

that structured stimulation mitigates the risk of sensory deprivation in patients with severe disturbances in consciousness and may facilitate neuroplasticity.<sup>43,44</sup> Mitchell and colleagues<sup>50</sup> investigated the effect of a Coma Arousal Procedure (CAP) in which sensory stimuli were presented through all 5 modalities at “greatly heightened frequency, intensity, and duration.” Subjects were 23 patients with severe traumatic brain injury who showed no purposeful movement and were unable to follow commands. Twelve subjects were assigned to the CAP treatment group. The remaining 12 subjects comprised the no-CAP control group and were matched according to age, sex, and type and location of injury. The CAP was administered 1 to 2 hours a day by trained family members for 7 to 12 days and the primary outcome was the time to recovery of command-following and purposeful movement. Coma duration was reported to be significantly shorter for the CAP group (mean difference = 5 days) in comparison with the control group. Because the sample was small and coma duration was not specified for either group, the shorter duration of coma noted in the CAP group may have been secondary to a few outlying scores in either group.

Thalamic deep brain stimulation (DBS) has been proposed as a method to improve arousal regulation in patients with DOC who retain functionally connected but downregulated or inconsistently active neural networks.<sup>51</sup> A double-blind alternating crossover study of DBS targeting central thalamic projections to the cortex demonstrated significant functional improvements in a 36-year-old man who remained in MCS for 6.5 years after sustaining severe traumatic brain injury during an assault. In this controlled study, performance on measures of arousal, motor control, and dysphagia was significantly better during periods in which DBS was turned on. Unexpectedly, performance remained well above baseline across all outcome measures after DBS was turned off, suggesting carryover effects.<sup>25</sup> Although the potential for deep brain stimulation and other neuromodulatory treatments to foster improvement beyond the period of spontaneous recovery is encouraging, additional large-scale trials are required to replicate preliminary findings, identify characteristics of responders versus nonresponders, and refine the technology.

## SUMMARY

The pace of research on DOC has advanced rapidly over the past 15 years. The availability of clear, behaviorally defined differential diagnostic criteria has enabled clinicians and researchers to distinguish patients who retain some elements of conscious awareness (ie, MCS) from those who are completely unconscious (ie, VS). A growing body of evidence indicates that there are key pathophysiologic differences between VS and MCS that predispose to significant differences in functional outcome and probability of response to treatment. Standardized behavioral assessment strategies for detection of conscious awareness are improving the reliability and validity of bedside assessment but may be confounded by concomitant sensory and motor impairments. Specialized structural and functional neuroimaging technologies, including diffusion tensor imaging and fMRI activation paradigms, are beginning to provide novel information concerning the integrity of neural networks that mediate arousal and cognition. As these procedures enter the clinical mainstream, they are likely to improve diagnostic and prognostic precision and may help tie treatment interventions to underlying pathophysiologic profiles. The development of treatments for patients with DOC has lagged behind advances in assessment, leading to a proliferation of pharmacologic and nonpharmacologic interventions with uncertain efficacy and adverse event records. A clearer picture of the risks and benefits associated

with particular treatments is expected to emerge over the next 5 years as the results of recently launched multicenter randomized controlled trials are made available.

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