Published in: Journal of the American Medical Directors Association (2015), vol. 16, issue 1, pp. e9-85.e14
DOI: 10.1016/j.jamda.2014.10.014
Status : Postprint (Author's version)

The Vegetative State: Prevalence, Misdiagnosis, and Treatment Limitations

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KEYWORDS*:* Long-term care; Vegetative state; Ethics; Acquired brain injury; Rehabilitation

ABSTRACT

Introduction: Patients in a vegetative state/unresponsive wakefulness syndrome (VS/UWS) open their eyes spontaneously, but show only reflexive behavior. Although VS/UWS is one of the worst possible outcomes of acquired brain injury, its prevalence is largely unknown. This study's objective was to map the total population of hospitalized and institutionalized patients in VS/UWS in the Netherlands: prevalence, clinical characteristics, and treatment limitations.

Methods: Nationwide point prevalence study on patients in VS/UWS at least 1 month after acute brain injury in hospitals, rehabilitation centers, nursing homes, institutions for people with intellectual disability, and hospices; diagnosis verification by a researcher using the Coma Recovery Scale-revised (CRS-r); gathering of demographics, clinical characteristics, and treatment limitations.

Results: We identified 33 patients in VS/UWS, 24 of whose diagnoses could be verified. Patients were on average 51 years old with a mean duration of VS/UWS of 5 years. The main etiology was hypoxia sustained during cardiac arrest and resuscitation. More than 50% of patients had not received rehabilitation services. Most were given life-sustaining treatment beyond internationally accepted prognostic boundaries regarding recovery of consciousness. Seventeen (39%) of 41 patients presumed to be in VS/UWS were found to be at least minimally conscious.

Conclusions: Results translate to a prevalence of 0.1 to 0.2 hospitalized and institutionalized VS/UWS patients per 100,000 members of the general population. This small figure may be related to the legal option to withhold or withdraw life-sustaining treatment, including artificial nutrition and

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hydration. On the other hand, this study shows that in certain cases, physicians continue life-prolonging treatment for up to 25 years. Patients have poor access to rehabilitation and are at substantial risk for misdiagnosis.

The vegetative state, recently renamed "unresponsive wakefulness syndrome" (VS/UWS),[1] is one of the worst possible outcomes of acquired brain injury. A patient in VS/UWS opens his or her eyes spontaneously, but shows no signs of consciousness; only reflexive responses to the outside world are seen.[2,3] Although often a transitional state in the process of recovery,[4] certain patients remain in VS/UWS for the rest of their lives, sometimes decades after the causative event.

The differential diagnosis of VS/UWS includes the locked-in syndrome in which the patient is fully conscious while incapable of speech and most motor reactions due to near-complete paralysis,[5,6] and the minimally conscious state (MCS), characterized by at least one sign of consciousness but absence of functional communication and functional use of objects.[7] Bruno et al[8,9] recently argued to distinguish patients who reproducibly follow commands (MCS+) from those who do not (MCS-).

Although the neurophysiological substrates of disorders of consciousness are steadily being unravelled,[10] their epidemiology remains unclear. In many countries, including the United States and Great Britain, the prevalence of VS/UWS is unknown.[11] A recent systematic review of prevalence studies on VS/UWS yielded 14 publications with a wide variation in both outcome (0.2-6.1 patients per 100,000 members of the general population) and methodological quality.[12]

Uncertainty about the exact number of people in a condition referred to as "a fate worse than death"[13] not only compromises our scientific picture, it also can be a barrier to the provision of the specialized health care these patients and their families need. In 2003, a Dutch prevalence study resulted in what appears to be the lowest reported prevalence of VS/UWS in the world: 0.2 patients per 100,000 members of the population.[14] However, it targeted the nursing home population exclusively and verified only a small subset of cases, whereas it has been shown that up to 43% of patients presumed to be in VS/UWS turn out to be at least in MCS when examined with a validated assessment tool.[15,16]

This article describes a point prevalence study of VS/UWS carried out nationwide in hospitals, nursing homes, hospices, facilities for people with intellectual disability (ID), and rehabilitation centers in the Netherlands.

Methods

The Netherlands is inhabited by 16.7 million people and has a population density of 401 people per square kilometer[17] (in comparison, the United States has a population density of 33.7 per square kilometer[18]). Medical aid, including long-term care, is available for all citizens and reimbursed through a dually financed insurance system. Nursing homes are staffed by specialized medical doctors, called elderly care physicians.[19]

In the last week of April 2012, we contacted medical directors from all of the 635 nursing homes (merged in 187 organizations); 20 rehabilitation centers; 90 hospitals with an intensive care unit,

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neurology, and/or neurosurgery ward; and 70 hospices, plus the 270 members of the Dutch Association of ID Physicians via e-mail. The e-mail provided the internationally established diagnostic criteria for VS/UWS.[3] The addressee was asked whether any patients with this diagnosis at least 1 month after acute brain injury (eg, hypoxia, stroke, trauma) were present within the population under the responsibility of the medical staff on May 1, 2012. Replies were given by e-mail. If a missing response could not be retrieved by telephone, the institution or physician was considered a nonresponder.

Representatives, mostly family members, of all patients reported received an information letter about the study and were asked for written informed consent. On permission, one researcher (WvE) assessed the level of consciousness by means of the Coma Recovery Scale-revised (CRS-r), a validated instrument for bedside determination of the level of consciousness in the post-acute setting.[20,21] Staff and family were invited to the assessment. Any additional behavior possibly indicative of consciousness they mentioned, for example command-following exclusively on request of a relative, was evaluated for contingency in a structured manner.[22] We documented medication, factors of possible influence on the level of consciousness (eg, infections) that had occurred up to 2 weeks before the study visit, and asked whether staff or family thought that the patient's state was any different from his or her normal condition. The time between the last administration of artificial nutrition and hydration (ANH) and the start of the assessment was registered, as patients have been shown to be less responsive shortly after administration of ANH.[23] The treating physician was requested to complete a secured online questionnaire about demographic and clinical characteristics, treatment goals, and limitations to treatment (eg, a do-not-resuscitate order). To prevent research participation from interfering with the relationship between the patient's proxies and the treating physician, study findings were communicated only to the latter. The families were notified of this before they gave consent.

STATISTICS

From the sum of the absolute number of verified and unverified cases of VS/UWS, a prevalence figure of hospitalized and institutionalized VS/UWS patients per 100,000 members of the Dutch population was calculated. Clinical characteristics were analyzed using SPSS 20.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). We calculated means, medians, confidence intervals, SDs, and percentages where applicable.

ETHICAL APPROVAL

According to the Dutch Medical Research Involving Human Subjects Act (1998), the study did not meet criteria for medical scientific research. The protocol was judged by an accredited medical research ethics committee, which on these grounds decided that no additional ethical evaluation was indicated. Nevertheless, the families of all patients were asked for written informed consent.

Results

Response rates were 96% for nursing homes, 100% for rehabilitation centers, 97% for hospitals, 53% for hospices, and 20% for ID physicians.

A total of 53 patients were reported to be in VS/UWS for at least 1 month after sustaining acute brain

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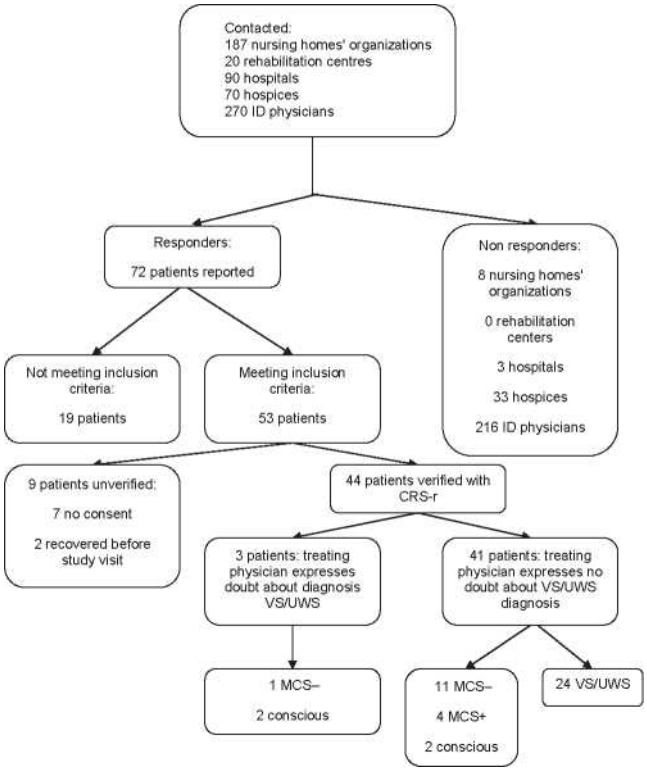
injury. Representatives of 46 of them consented to inclusion. The patients were visited with a median time lapse from the point prevalence date of 20 days: 30 patients were seen within 30 days, 14 patients between 30 and 60 days and 2 after over 60 days. We obtained CRS-r scores in all 46 patients. In 38 cases, additional behavior was reported by medical staff or families and evaluated for contingency. Among the observed personally salient stimuli were proxies' voices, music, family pictures, the smell of chocolate, the presence of a patient's dog, and watching a stand-up comedian on TV. Results of the initial inquiry and of the verification are shown in Figure 1.

On the day of verification, 2 patients were reported by their physician to have emerged from VS/UWS since the point prevalence date. Both had sustained neurological damage due to subarachnoid hemorrhage. According to their respective physicians, one had been in VS/UWS up until 2 months after the incident (4 days after the point prevalence date), and the other up to 10 months (30 days after the point prevalence date). Testing by means of the CRS-r confirmed MCS+ in both patients. Combined with the 7 cases in which we obtained no consent, this resulted in 9 unverified cases. Thus, the diagnosis could be verified in 44 patients. Six patients had recently had infections, seizures, or other events possibly influencing level of consciousness, 15 were on medication with sedative side-effects, and 13 patients were assessed within 1 hour after the administration of artificial nutrition.

In 24 of 44 individuals, CRS-r assessment confirmed the diagnosis of VS/UWS. In 3 other cases, the treating physician expressed doubts about the diagnosis. One of these patients was found to be in MCS-, the other 2 were conscious, as demonstrated by the ability of functional use of objects and/or functional communication (Table 1).

Figure 1. *Flowchart showing results of prevalence inquiry and verification.*



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Seventeen of 41 patients with a reported clinical diagnosis of VS/UWS (39%) showed signs of consciousness: 11 were in MCS-, 4 in MCS+, and 2 were conscious (Table 2). All signs of consciousness were detected by means of the CRS-r, with the exception of one patient who reproducibly showed a distinctive facial expression and vocalization when presented with an ice cream. The other patients' conscious behavior had not been witnessed by staff before (eg, communication only with a nephew) or had been seen but not been recognized as a sign of consciousness (eg, visual following of a mirror). The proportion of families who agreed with the diagnosis of VS/UWS was nearly the same for misdiagnosed and confirmed VS/UWS patients (45% versus 50%, respectively).

The 24 verified and additional 9 potential cases resulted in a total of 24 to 33 hospitalized and institutionalized patients in VS/UWS in the Netherlands, or 0.1 to 0.2 for every 100,000 members of the general Dutch population on May 1, 2012.[24]

PATIENT CHARACTERISTICS

Basic characteristics are shown in Table 3. Notably, half of the total patient group (12/24) was in VS/UWS due to postanoxic encephalopathy following cardiac arrest and resuscitation. Tracheostomy was present in 8 cases (33%); 5 were cuffed, 3 noncuffed. This group had sustained the causative injury relatively recently (mean 1 year, 8 months) when compared with the group without tracheostomy (mean 6 years, 8 months). All patients received ANH via percutaneous endoscopic gastrostomy, except for one patient with a nasogastric tube. Her physicians had decided to refrain from new medical interventions soon after the causative event, 3 years before. None of the individuals were on respiratory support, 7 (29%) had a urinary catheter. There were no pressure sores.

Four patients (17%) were within internationally accepted prognostic boundaries, this is, 3 months after nontraumatic and 12 months after traumatic causes.[3] The other 20 patients had been in VS/UWS for on average 6 years (SD 6 years 2 months); 3 nontrauma for 3 to 12 months, 9 for 1 to 5 years, 5 for 5 to 10 years, and 3 for more than 10 years. One patient had suffered traumatic brain injury at age 18, and was now 43.

None of the patients had a known advanced care directive. The treatment goal was defined as "palliative" (ie, aimed at quality of life, may include life-prolonging therapies) in 13 patients, "curative" (ie, aimed at recovery of consciousness) in 5 patients, "symptomatic" (ie, aimed at quality of life, excluding life-prolonging therapies) in 3, and "other" in 3 patients. Treatment limitations were in place in 19 patients (79%): 19 were not to be resuscitated, 16 were not to be intubated, 11 were not to be readmitted to the intensive care unit, and 9 were not to be readmitted to hospital in general. In 4 patients, the treating physician expressed the intention to withdraw medical treatment, including ANH. On the other hand, 4 of the aforementioned patients who were beyond chances of recovery had no treatment limitations at all.

On the study date, 2 patients were still in hospital. Of the remaining 22 individuals admitted to long-term care facilities, only 10 (46%) were or had been enrolled in either a specialized (ie, sensory stimulation therapy[25]) or regular rehabilitation program.

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Discussion

To the best of our knowledge, this is the first prevalence study on VS/UWS carried out nationwide in all health care sectors and aiming at 100% diagnosis verification by means of the CRS-r. We found an overall prevalence of 0.1 to 0.2 hospitalized and institutionalized VS/UWS patients per 100,000 inhabitants. As mentioned, a Dutch prevalence study performed in 2003 yielded a similar figure, although this was limited to the nursing home population and with diagnosis verification in only 9.4% of cases.[14] When comparing the 2003 results with the present, the most striking difference is in etiology. Whereas stroke accounted for 47% of VS/UWS cases 10 years ago, in the current population it is the causative injury in only 13%. Instead, the major cause of VS/UWS (50% of patients) is now hypoxic brain injury, whereas in 2003, this was the etiology in merely 23%. Notably, none of the patients had any reported pressure sores. This can be seen as a mark of the level of care and caring provided to the patients in these settings in the Netherlands.

Table 1 - *Signs of Consciousness in Patients With Doubtful Diagnosis*

Treating Physician's Diagnosis	Consensus; Agreement on Diagnosis Between Staff and Proxies	Coma Recovery Scale-revised	Structured Observation	Researcher's Diagnosis
Doubt	No: proxies consider behaviour to be *reflexive,* staff has doubts	Object manipulation	Manipulates poker chips exclusively	MCS-
Doubt	No: proxies and physical therapist consider movements to be nonreflexive, physician has not witnessed this	Reproducible movement to command, functional use of object (spoon) only on request of proxy	No additional findings	Conscious
Doubt	No: proxies experience functional verbal communication, staff has not witnessed this	Functional communication only with nephew	No additional findings	Conscious

MCS-, minimally conscious state in which patients do not reproducibly follow commands.

Considering methodological factors and the shortage of reliable figures from other countries, the prevalence of VS/UWS in the Netherlands seems relatively low.[11,12] This may be attributable to end-of-life decisions in the acute phase of severe brain injury,[26] as well as in post-acute and long-term care settings.[27] In the 1990s, an ethical, medical, and legal framework was established in the Netherlands stating that life-sustaining treatment, including ANH, for the sole purpose of prolonging VS/UWS beyond chances of recovery of consciousness is medically futile[28,29] and violates human dignity.[30] In practice, withdrawal of ANH is allowed beyond 3 to 6 months after nontraumatically and 12 months after traumatically induced VS/ UWS. The decision to withhold or withdraw medical treatment is made by the physician.[30,31] Still, in 20 of 24 patients in our study, life-sustaining treatment was continued beyond these prognostic boundaries. In other words, despite the legal option of ANH withdrawal, Dutch doctors do continue treatment, in certain cases for more than 25 years. The finding that many families disagree with the diagnosis of their loved one in VS/UWS is likely to influence medical decision-making. Earlier publications suggest the absence of advanced

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care directives to play a crucial role in these processes, as well.[31,32]

Table 2 *- Signs of Consciousness in Misdiagnosed Patients*

Treating Physician's Diagnosis	Consensus; Agreement on Diagnosis Between Staff and Proxies	Coma Recovery Scale-revised	Structured Observation	Researcher's Diagnosis
VS/UWS	Yes	Visual following	No additional findings	MCS–
VS/UWS	Yes	Visual following	No additional findings	MCS–
VS/UWS	Yes	Visual following	No additional findings	MCS–
VS/UWS	Yes	Visual following	Laughs appropriately during stand-up comedian's conference on TV	MCS–
VS/UWS	Yes	Reflexive behavior	Smiles in response to ice cream, screams when ice cream is removed, smiles when returned 4/4 trials	MCS–
VS/UWS	Yes	Localization of noxious stimuli	Fumbles with sheet	MCS–
VS/UWS	No: proxies experience eye contact	Visual following	No additional findings	MCS–
VS/UWS	No: proxy experiences functional communication by means of sighs and facial expression	Visual following	No additional findings	MCS–
VS/UWS	No: proxies experience eye contact	Visual following, automatic motor response	No additional findings	MCS–
VS/UWS	No: proxies and nurses consider ball catching nonreflexive	Object localization (reaching), localization of noxious stimuli	Catches a ball thrown horizontally from 2 m distance	MCS–
VS/UWS	No: paramedics consider reactions to visual stimuli to be nonreflexive	Object recognition, automatic motor response	No additional findings	MCS–
VS/UWS	Yes	Reproducible movement to command, visual following, object manipulation, intentional communication when asked for by proxy	No additional findings	MCS+
VS/UWS	Yes	Reproducible movement to command, visual fixation	Visual fixation on children's picture	MCS+
VS/UWS	No: proxies consider smiles to be nonreflexive	Reproducible movement to command, object recognition	Shakes researcher's hand	MCS+
VS/UWS	No: proxies experience eye contact	Reproducible movement to command, object localization (reaching), automatic motor response	No additional findings	MCS+
VS/UWS	Yes	Consistent movement to command, object recognition, functional use of object (toothbrush), functional communication when asked for by proxy	No additional findings	Conscious
VS/UWS	No: proxies and speech therapist report functional use of objects and command following, unwitnessed by physician	Systematic movement to command, object localization (reaching), functional use of objects (spoon, toothbrush) only on request of speech therapist	No additional findings	Conscious

MCS-, minimally conscious state in which patients do not reproducibly follow commands; MCS+, minimally conscious state in which patients reproducibly follow commands; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

Remarkably, one of the patients in this study was reported to have emerged from VS/UWS 10 months after the occurrence of nontraumatic brain injury. Recent publications show that the aforementioned prognostic boundaries may be outdated.[33] Our methods, however, were not designed to assess VS/UWS prognosis. Another unexpected finding was the absence of children in our population. It might be that parents prefer to care for them at home, organizing professional support through the system of personal care budgets provided by the Dutch government.

In the Netherlands, clinical rehabilitation for disorders of consciousness is reimbursed only for patients up to the age of 25. Older individuals are sometimes accepted to a similar program in 1 of 2 dedicated nursing homes, which receive no financial coverage from health insurance companies and therefore have limited capacity. The consequences are reflected in our study: 54% of patients had been admitted directly to a long-term care facility without going through any form of rehabilitation. Although the effects of specialized rehabilitation for disorders of consciousness have not been established in a randomized controlled setting,[34] the fact that a country allows cessation of treatment without enabling patients to first fully explore their means of recovery raises questions.

Seventeen (39%) of 44 patients considered to be in VS/UWS turned out to be in MCS or were even conscious when examined with the CRS-r. For the first time, diagnostic accuracy of VS/UWS has been examined in long-term care facilities.

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Table 3 *- Basic Characteristics of Patients With Verified Vegetative State/Unresponsive Wakefulness Syndrome*

Sex, n (%)	Female: 12 (50) Male: 12 (50)
Age, y	
Mean (SD)	51 (13)
Range	27-73
Marital status, n (%)	Single: 9 (38) Married: 12 (50) Partner, unmarried: 3 (12)
Location, n (%)	Nursing home: 20 (83) Institution for people with intellectual disability: 2 (9) Hospital: 2 (9) Rehabilitation center: 0 (0) Hospice: 0 (0)
Time lapse since incident	
Mean (SD)	5 y (6 y)
Range	1 mo-25 y
Etiology, n (%)	Nontraumatic: 16 (67) Traumatic: 7 (29) Both: 1 (5)
Causes of hypoxic encephalopathy	Cardiogenic shock: 7
(n = 12) (includes patient with both traumatic and nontraumatic etiology)	Septic shock: 2 Hypovolemia: 1 Accidental asphyxia: 1 Unknown: 1
Other nontraumatic causes (n = 5)	Subarachnoid haemorrhage: 3 Tuberculous meningitis: 1 Dengue fever and overcorrection of hyponatremia: 1
Traumatic causes (n = 8) (includes patient with both	Traffic accident: 6

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traumatic and nontraumatic etiology)	Fall: 2

Our results correspond to previous studies on the diagnostic accuracy of VS/UWS in hospitals and rehabilitation centers.[15,16] The difference between VS/UWS and MCS is of considerable clinical relevance. Patients in MCS have a better chance of recovery than VS/UWS patients[35-38] and appear to process emotional, auditory, and nociceptive stimuli in a way very similar to that of healthy individuals.[39,40] Underestimating their level of consciousness may have serious consequences in terms of prognosis, access to rehabilitation, analgesia, and end-of-life decisions. In some cases we assessed, subtle signs of consciousness seem to have gone unnoticed by staff. This is particularly understandable when it comes to eye tracking or responses occurring only in reaction to very specific stimuli. In others, conscious behavior was wrongfully labeled reflexive, such as in the patient who had for years been able to catch a ball. Only one of the institutions we visited used a specific scale for level of consciousness assessment in the post-acute phase: a nursing home with a specialized rehabilitation ward, where the Western Neuro Sensory Stimulation Profile[41] was administered. Unfamiliarity with MCS as a distinct clinical condition and the rareness of prolonged disorders of consciousness may give rise to misdiagnosis as well.

There are limitations to this study. Although high response rates were obtained from hospitals, nursing homes, and rehabilitation centers, we cannot ignore the possibility of underreporting, especially from hospices and facilities for people with ID. Missing responses from these sectors could not be pursued, because many Dutch hospices are staffed by consultants, and because of the absence of a central registry of ID facilities. It is also imaginable that some negative responses were incorrect; that is, respondents based their reply on incomplete information. If this were the case, the actual number of patients may be higher. On the other hand, a more extensive verification protocol might have detected signs of consciousness in certain patients, specifically those in whom factors like infections, sedatives, and recent administration of ANH were present. Still, our single-observer on-site verification method covered a complete country within a median of 20 days after the point prevalence date. The active involvement of patients' proxies and staff enriched the assessment: in all but one of the cases in which proxies disagreed on the treating physician's diagnosis of VS/UWS, the family and/or a nurse who knew the patient well were present.

Recommendations

Providing good care for patients with a rare, complex condition in a context of scattered expertise, paucity of diagnostic and therapeutic guidelines, and scarce resources is challenging. Nonetheless, patients with disorders of consciousness deserve tailored medical care in accordance with up-to-date scientific and psychosocial standards. Our study shows that at this moment, patients in VS/UWS and related conditions are at substantial risk of being misdiagnosed and of being denied rehabilitation. The number of patients appears to be too small for nonspecialized health care institutions to gather and retain adequate experience and expertise.

We suggest the installation of a readily accessible network of experts providing on-site diagnostic, prognostic, and therapeutic advice to staff, monitoring level of consciousness by means of the CRS-

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r and complementary diagnostics. A network like this also could ensure liaison between hospitals, rehabilitation centers, and nursing homes and guide families along the process. Future research should concern patients being cared for at home and in ID facilities, long-term outcomes, as well as factors contributing to the apparently low prevalence of VS/UWS in the Netherlands. Until medical science finds a cure for the severest outcomes of acquired brain injury, this seems to be the least that could, and should, be offered to patients with prolonged disorders of consciousness and their families.

Acknowledgments

We thank the SBOH for making this research project possible. Our gratitude also goes out to all cooperating physicians, and to the patients and their families who were involved in this study.

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Published in: Journal of the American Medical Directors Association (2015), vol. 16, issue 1, pp. e9-85.e14
DOI: 10.1016/j.jamda.2014.10.014
Status : Postprint (Author's version)

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