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Prolonged disorders of consciousness: A response to a "critical evaluation of the new UK guidelines."

Derick T Wade[1], Lynne Turner-Stokes[2], E Diane Playford[3], Judith Allanson[4], and John Pickard[5]

Abstract

Background: In 2020, The London Royal College of Physicians published "Prolonged disorders of consciousness following sudden-onset brain injury: national clinical guidelines". In 2021, in the journal Brain, Scolding et al. published "a critical evaluation of the new UK guidelines". This evaluation focussed on one of the 73 recommendations in the National Clinical Guidelines. They also alleged that the guidelines were unethical.

Criticisms: They criticised our recommendation not to use activation protocols using fMRI, electroencephalography, or Positron Emission Tomography. They claim these tests can (a) detect 'covert consciousness', (b) add predictive value and (c) should be part of routine clinical care. They also suggest that our guideline was driven by cost considerations, leading to clinicians deciding to withdraw treatment at 72 h.

Evidence: Our detailed review of the evidence confirms the American Academy of Neurology Practise Guideline (2018) and the European Academy of Neurology Guideline (2020), which agree that insufficient evidence supports their approach.

Ethics: The ethical objections are based on unwarranted assumptions. Our guideline does not make any recommendations about management until at least four weeks have passed. We explicitly recommend that expert assessors undertake ongoing surveillance and monitoring; we do not suggest that patients be abandoned. Our recommendation will increase the cost We had ethicists in the working party.

Conclusion: We conclude the "critical evaluation" fails to provide evidence for their criticism and that the ethical objections arise from incorrect assumptions and unsupported interpretations of evidence and our guideline. The 2020 UK national guidelines remain valid.

[1]Oxford Brookes University, Oxford, UK
[2]Cicely Saunders Institute, King's College London, London, UK
[3]Warwick Medical School, University of Warwick, Coventry, UK
[4]Department of Neurological Rehabilitation, Addenbrookes Hospital, Cambridge, UK
[5]Academic Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

Corresponding author:
Derick T Wade, 28 Polstead Road, Oxford OX2 6TN, UK.
Email: derick.wade@ntlworld.com

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Introduction

A recent article by Scolding et al.[1] reviewed the National Clinical Guideline, Prolonged Disorders of Consciousness Following Sudden Onset Brain Injury, recently published in the UK by the Royal College of Physicians (RCP).[2] The article focuses on one recommendation (2.7), which addresses the use of advanced imaging and EEG techniques. There are 72 other recommendations in the 2020 guidelines covering the life-long care pathway for patients with prolonged consciousness disorder (PDOC).

The criticism

The authors argue that *"by showing that a patient retains awareness and is able to communicate, albeit, in a rudimentary fashion, techniques like fMRI certainly represent practical steps towards helping the patient make a decision"*. They argue that failing to scan patients routinely using these techniques may be unethical. The same authors have since published a letter in the Times (30.7.2021)[3] claiming that *"Thousands of people labelled as being in a vegetative state are in fact fully, or at least partially, conscious but the guidance does not recommend the use of such technologies"* – a position that they claim to be indefensible on *'scientific, ethical and legal grounds.'"*

They also consider that the UK guidelines are out of step with the US guidelines from the American Academy of Neurology (AAN),,[4] which *'recommend the use of fMRI or advanced electrophysiological testing in certain circumstances*. The two recommendations (2e, 2f) are shown below.

AAN 2e

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

AAN 2f

In situations where there is no behavioural evidence of consciousness on clinical examination but functional neuroimaging or electrophysiologic testing suggests the possibility of preserved conscious awareness, frequent neurobehavioral reevaluations may be conducted to identify emerging signs of conscious awareness (Level C based on feasibility) and decisions to reduce the intensity of rehabilitation treatment may be delayed for those individuals receiving active rehabilitation management (Level C based on variation in patient preferences and cost relative to net benefit), with the length of time over which these are done determined by an agreement between the treating clinician and the health care proxy given the lack of evidence to provide guidance.

"Level C" evidence is equivalent to GRADE level C (Low Confidence),[5] and is given the verbal equivalent of "possibly" by the AAN.[6]

Context of AAN guidance

It is essential to place the US American Academy of Neurologists, guidance in the context of their healthcare system. In marked contrast to the UK healthcare system, the US system requires very early decisions about discharging patients from the acute hospital - within days or a few weeks.

Moreover, rehabilitation services are much more restricted in the US and work in short timeframes. A stay in a rehabilitation centre will be weeks, not months, with a strong focus on measurable change. Consequently, many patients are discharged to 'skilled nursing facilities' that do not have expertise in the initial assessment, continued monitoring and physical management of patients in a prolonged disorder of consciousness.

Context of UK guidance

The UK guidance comes from the RCP, London. It refers to the National Health Service (NHS) in England, which provides lifelong care that is free at the point of delivery. It is relevant to the other UK countries, which have broadly similar care provisions. The journey of a patient left with a prolonged disorder of consciousness will usually include a long (many weeks) admission to a neurosciences centre, followed by a few months in an in-patient rehabilitation centre. Patients remaining unconscious will then move to an NHS-funded specialist nursing facility and should have access to review by and, if necessary, input from an expert rehabilitation team. All this reduces the pressure for early prognostication and decision-making.

Scolding et al.[1] state, *"The guidance recommends that a standard clinical evaluation should include a detailed clinical history, a review of medication, and detailed neurological evaluation by an experienced clinician. After the clinical evaluation 'no standard or routine investigations are required for patients in PDOC'."* These two sentences under-represent the detailed guidance on the assessment, and ongoing monitoring of patients set out in 48 pages with 28 recommendations in Sections 2 and 3.

The UK guideline recognises that many patients in a prolonged disorder of consciousness during the first few weeks and months following a severe brain injury will emerge into consciousness, especially those who demonstrate a trajectory towards improved awareness. We now know that many of the patients who emerged from unconsciousness after years of being in 'persistent VS' showed signs of awareness in the earlier stages. For example, Terry Wallis, who had been thought to be in the vegetative state for 19 years, showed signs of inconsistent gestural communication compatible with the minimally conscious state (MCS) from just a few weeks post-injury.[7] This was before the condition of MCS had been described. The definition of MCS,[8] and its subsequent subdivision into MCS-minus and MCS–plus[9] have emphasised that recovery of awareness evolves.

Thus, the UK guidelines set out a detailed pathway of life-long care in five phases (Section 3 especially its Figure 3.1)) that include a thorough clinical evaluation by experts in assessing patients in a prolonged disorder of consciousness through serial assessment and monitoring over time. They specify an initial intensive period of 2–4 months in a specialist PDOC centre (Phase II). This period is followed by active management and ongoing assessment supported through outreach services from those centres in the first year (Phase III), with at least an annual review (Phase IV) until no further change occurs.

The US[4] and European guidelines[10] recommend basing clinical diagnosis on the Coma Recovery Scale - Revised (CRS-R) tool. In contrast, the UK guidelines support using three validated tools: the CRS-R, the Wessex Head Injury Matrix (WHIM) and the more detailed Sensory Modality Assessment and Rehabilitation Technique (`SMART'), which complement each other.[11] The guideline further recommends that all of this be recorded and monitored through a national registry to monitor implementation.

It is incorrect to say that the UK guidelines *"do not recommend the use of fMRI/EEG'*. The guidelines clearly state that *"these more advanced brain imaging and electrophysiology techniques have provided valuable insights into this patient group and will continue to provide an important focus for research… However, more work is required to understand how these investigations should be interpreted, whether they have any prognostic value, and how these findings could contribute to decision-making in the context of the other recommendations for evaluation and ongoing monitoring"*. The UK is an active contributor to the international multicentre prolonged disorder of consciousness and coma

research frameworks, including the James S McDonnell Foundation and the Neurocritical Care Society Curing Coma Campaign.

False-negative findings with activation studies

Scolding et al.[1] dispute the figure of up to 1 in 5 for false negatives with fMRI and EEG activation studies using spatial navigation and motor imagery in healthy volunteers. In Owen's experience, they state that only around 1% fail to generate fMRI activity in motor imagery tasks. However, his own group's study from 2014 reported that using 3 T MR, 3/14 healthy volunteers (21%) failed to show brain activity in some of their sessions or for one of the two tasks,[12] and 7/14 (50%) failed to show activation in the parahippocampal gyrus on the spatial navigation task.

Similar rates of negative responses have been reported by Edlow 2017[13] (31% negative on hand squeezing) and Bodien 2017[14] (hand squeezing 30%; tennis 10%). False negative rates of around 25% are also seen with electroencephalography.[13,15] Studies of brain-computer interface (BCI) show 10–31% of BCI users do not modulate their brain signals in a way required for BCI control, hence the somewhat unkind term 'BCI illiterate'[16,17] These rates of negative responses are not surprising given the complexities surrounding imaging motor imagery, such as prior experience, skill level, training, and visual versus kinesthetic tasks.[18]

Complexities surrounding activation studies

An early study reported a woman tested with an fMRI activation protocol six months after a traumatic brain injury.[19] Her data are also in a later paper,[20] which states that she later recovered consciousness.

This well-known paper[20] reported that five of 54 patients examined by fMRI showed apparent modulation of brain activity in response to verbal instructions. Four of the 23 patients diagnosed as in the vegetative state showed a response, while only one of 31 patients in the MCS did.

The points we draw attention to are:

(a) all five patients had traumatic brain injuries.
(b) three of the five patients were within 12 months of injury (1, 2, and 6 months).
(c) although not given in the results section, the discussion reveals that two patients had behavioural signs of awareness, but which two patients is not stated.

Scolding et al.[1] also rely on a study that involved 122 patients in a prolonged disorder of consciousness (four more had a locked-in syndrome).[21] The study compared the diagnosis of MCS or Vegetative State, based on the CRS-R, against (i) fMRI activation by command, (ii) positron emission tomography (PET) evidence of hypoactivation of brain areas, and (iii) clinical consensus. Stender et al.[21] found that only 59% of PDOC patients could be assessed with mental imagery fMRI leaving 41% (50/122) who could not be evaluated mainly because of spontaneous movement necessitating sedation before MRI.

They confirmed Monti et al.'s finding (1/33) of low sensitivity (45%) in MCS patients.[20] This may arise because mental imagery is too cognitively demanding. Patients may not have understood the task, had the drive to participate or lacked language and short-term memory. Much inconsistency was noted in diagnosis by different methods. They state, "*we detected brain activity deemed to suggest (minimal) consciousness with at least one neuroimaging modality in 13 of 41 (32%) patients diagnosed with unresponsive wakefulness syndrome*." They also note that active fMRI "*seems to be less accurate*." The population studied had a mean age of 41 years, and it is unlikely to have been representative of the overall population experiencing prolonged disorders of consciousness.

In contrast, Scolding et al.[1] suggest that fMRI is now a straightforward technique adopted in clinical MR facilities using either 1.5 T or 3 T scanners.[12] We, in Cambridge (JA & JDP), agree with Stender[21] that '*Functional neuroimaging has*

important limitations. The image acquisitions are expensive, technically challenging and logistically complicated. Additionally, statistical analysis is complex and contains a risk of false outcomes'. Only 43% (9/21) of patients who demonstrated command-following on EEG did so with fMRI.[22]

Owen's group echoed these sentiments as they moved toward EEG studies: '*Use of fMRI in this patient group is very challenging: in addition to issues of cost and scanner availability, the physical stresses incurred by patients when they are transferred to suitably equipped fMRI facilities are substantial. Movement artefacts often occur in imaging data sets from patients who are unable to remain still, and metal implants, including plates and pins, which are common in many traumatically injured populations, can completely rule out use of fMRI*'.[15]

Scolding et al. also refer to a study of 104 patients with acute brain injury seen in intensive care assessed at a median of six days after onset.[23] This is not relevant to the UK guidelines because they only apply to patients after four weeks.

In another study used by Scolding to justify investigation, electroencephalographic (EEG) data was collected from 113 patients, using various analyses to determine responses to stimuli and the complexity of the EEG.[24] An automatic classification algorithm was developed. The authors give little clinical information, and some patients had multiple evaluations. The main points to note are:

(a) the automatic classification system classified 38 recordings from conscious, healthy (n = 4), or brain-injured people as being in a vegetative or minimally conscious state;
(b) 25 of the 75 recordings from people classified clinically as being in a vegetative state were classified as minimally conscious by EEG;
(c) 16 of the 68 recordings from people classified clinically as minimally conscious were classified as in the vegetative state by EEG;
(d) there was a slightly greater probability of improvement from a vegetative state to a minimally conscious or conscious state if the EEG suggested a minimally conscious state.

While we agree that EEG may eventually become a research tool, we cannot recommend it for routine clinical use in the UK.

In the discussion, Scolding et al. take issue with the value of Diffusion Tensor Imaging and ^{18}F-FDG PET over activation fMRI, saying, '*there is no evidence these techniques have any clinical application in the context of PDOC*'.

On the contrary, two studies have revealed that some 90% of PET studies were completed in the PDOC patients studied. For example, in Stender's study,[21] of 126 patients, 92% had successful PET scans; congruence with the unresponsive wakefulness syndrome was 67%; sensitivity for the MCS was 93%, and overall outcome prediction outcome was 74%. A recent study on 52 patients also found reasonable accuracy.[25] Although encouraging, the accuracy and validity of PET scans to **diagnose** the level of awareness needs much further research before routine use can be recommended.

The last specific evidence used by Scolding came from a systematic review of studies investigating evidence suggesting preserved consciousness in people diagnosed with a prolonged disorder of consciousness.[26] The paper reports that:

(a) the studies included in the review were at a relatively high risk of bias
(b) active paradigms, where the patient is asked to do something, maybe more specific
(c) there are associations between 'positive' results and clinical assessments, but there is significant inconsistency at an individual patient level.

In their discussion, Scolding et al.[1] make several further statements not supported by the evidence they used. For example, they state that "*functional neuroimaging could predict recovery from VS with 93% specificity and 69% sensitivity*" The evidence given came from 15 studies with only 48 patients,

most being single cases, with two different techniques being used to predict recovery.[27]

As a second example, they state, "*A more recent EEG-based study indicated that 40% of VS/UWS patients were able to follow commands consistently enough to be classified as aware.*" This study included 78 patients, most seen within the expected recovery period for their pathology.[28] Only 3 of the 34 with 'positive' findings were outside this period. Moreover, the study aimed to study the predictive value of an EEG response to specific stimuli; it did not investigate the presence of awareness. The measure of awareness was statistical (percentage correct), and it was not based upon evidence of a specific response to a particular stimulus.

Evaluation of evidence used

The papers used as evidence in the "critical evaluation" all have significant weaknesses, limiting the conclusions drawn from them individually and collectively. The critical flaws are:

(a) Study samples are heterogeneous, particularly in terms of time since the onset of the condition, such that many patients seen are in a phase of recovery.
(b) None of the primary studies meets the accepted criteria for observational studies (STROBE[[29]) or prognostic and diagnostic studies (STARD[30]).
(c) Some studies give limited clinical information, making interpretation difficult.
(d) One study used to support undetected awareness (a) was studying prognosis, not the diagnosis of awareness, and (b) did so on a statistical basis, with no criterion to diagnose awareness.

We think that the authors have over-interpreted and misinterpreted the evidence they use to support their arguments in at least one case. We do not accept the criticism that we under-value and unreasonably dismiss the use of technologically-based investigation. We think that:

(a) at present, such investigations can and should be used in research;
(b) if research provides sufficient evidence, then studies comparing their findings compared directly against the most appropriate clinical results will be needed to assess a test's utility;
(c) recommending the use of a test also needs to consider (a) how practical and available the test will be for all patients who might need it and (b) the context of the other UK guidance recommendations for detailed and ongoing evaluation.

Their discussion

Their discussion raises three other matters (diagnosis, ethics, influence of costs) but fails to discuss one vital issue.

The fundamental issue **not** discussed, central to the article, is how awareness is determined or validated? This is not a trivial question. The CRS-R is an excellent and valuable measure that does what it says - it measures recovery from coma. It is a wonderful simple tool for serial monitoring of any trajectory towards a change in the level of responsiveness. It does not replace detailed clinical evaluation by experts in assessing consciousness. We recognise that the whole question of 'what is consciousness?' is open to scientific and philosophical debate. Nonetheless, if dogmatic statements are to be made about patients and their level of awareness, some evidential justification is needed.

One theme in Scolding article is misdiagnosis, repeating the oft-quoted figure of 40%—most of this 'evidence' concerns categorising patients into the vegetative or MCS.[31,32] One reason for using the term prolonged disorder of consciousness is that clinicians who work in the field understand that the levels of consciousness form a spectrum.[31] Defined 'cut-offs' have limited value, especially as the level of responsiveness is known to fluctuate over time. Misdiagnosis of the locked-in state as a prolonged disorder of consciousness happens but rarely, and it is unreasonable to claim 40% misdiagnosis. The UK guidelines emphasise the need for assessment by trained, expert clinicians with monitoring over months or years if necessary.

Scolding et al.[1] also discuss ethics. The UK working group discussed ethical aspects, had input from experts in moral matters, and circulated the document widely for comment. We acknowledge the ethical aspects of managing patients with a prolonged disorder of consciousness within the document.

Scolding et al. bring up several ethical issues based on two assumptions: that the findings reveal 'covert awareness'; and that the investigation allows clear communication about cognitively and emotionally challenging matters. We have discussed the first assumption, and they give no evidence showing that one can establish consistent and dependable communication.

Even if it is accepted that a few patients have, on a few occasions, answered simple yes/no questions correctly, it is implausible that one can obtain reliable information. There is a significant risk of misinterpreting indirect methods of communication.[33–35] Being able to respond to specific commands, such as thinking about moving their arms or legs whilst in a scanner, is very different from appreciating cause and effect. It certainly does not imply a patient understands their situation and prognosis and can respond to complex and abstract questions about their current and future care. Patients who have been in a prolonged disorder of consciousness for many months following a severe acquired brain injury will inevitably have ongoing physical and cognitive deficits if they emerge into consciousness. Very few will ever recover the mental capacity to make decisions regarding their care and treatment.

Scolding et al.[1] also claim that *"Not to scan conscious patients is to abandon them. This abandonment could result in life-preserving treatment and tube-feeding being withdrawn. Accurate prognosis is important, as most decisions to withdraw life-preserving treatment are made within 72 h of injury"*.

While this may or may not be the case in acute settings, it is irrelevant to these guidelines for 'Prolonged Disorders of Consciousness', which, by definition, do not start until at least four weeks after injury. The strong presumption favouring prolonging life for patients in PDOC in the UK makes decisions to withdraw tube-feeding still relatively rare. With the detailed assessment required during the decision-making process, a decision about limiting or removing treatment will usually occur several months (and often years) after the initial brain injury.

Moreover, according to the Mental Capacity Act 2005 in England and Wales, decisions to continue/withdraw life-sustaining treatment are not determined by the patient's current or future level of consciousness. Decisions centre on whether the patient will regain a quality of life that they would value – a decision that encompasses a more comprehensive range of considerations.

However, we have ethical concerns about 'false negatives' on the suggested tests. Patients categorised as in a MCS may not show any activation on fMRI.

Scolding et al.[1] argue that false negatives do not matter as the patients have already shown some level of awareness, however inconsistent. They say that positive results influence action in patients classified as vegetative state/unresponsiveness wakefulness syndrome on the CRS-R. *"If a scan in this group shows no evidence of consciousness, the patient is no worse off. If, by contrast, a scan would have detected consciousness but is not performed, the patient is significantly worse off."* They do not expand on how such patients in the UK would be worse off. Decisions are not based on the categorisation of consciousness.

We are aware of proposals, not in the UK, about using activation fMRI and EEG as the basis for making decisions about stopping intensive care, rehabilitation and artificial nutrition and hydration. In these circumstances, patients in a prolonged disorder of consciousness who were "activation scan negative" could be worse off depending on their prior wishes. Some of these scan-negative patients will emerge from their unconsciousness. The UK guidelines would not cut short this recovery.

The authors also imply that our recommendations are unreasonably influenced by considering costs and practicality. We think practicality must be considered, if only from a perspective of equity. It is unreasonable to recommend something to apply to many people if only a few per cent can benefit from it.

On the other hand, the cost was not a primary consideration in limiting recommendations. Indeed, many of our recommendations require more resources

than are available, and we continue to campaign for them. Second, there was much debate about the risk that, recommending a first-class service for this group of patients, many other patients who need rehabilitation input would receive even less than they do now.

We, therefore, do not accept the ethical criticisms. They are either based on clinical assumptions that are unfounded and implausible or on a failure to consider the complete guideline.

Conclusion

We are glad that Brain considered the guidelines needed discussion. We are disappointed that the reviewers focussed on a minor part of the guideline, ignoring the broader recommendations and context, and based on partial and unjustified interpretation of the evidence presented. We agree that advanced imaging and electrophysiological techniques may potentially have a future role in managing PDOC patients. Still, more information is needed to understand the added value of these techniques in the context of detailed long-term clinical evaluation as recommended in the RCP guidelines. We stand by the recommendations that these investigations should only be undertaken as part of a registered research programme. We hope that readers will look at the guideline and find it helpful across the whole pathway from four weeks after the onset of an acute condition leaving someone in a prolonged disorder of consciousness, potentially for the rest of their life.

Declaration of conflicting interests

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ORCID iDs

Derick T Wade https://orcid.org/0000-0002-1188-8442

E Diane Playford https://orcid.org/0000-0001-7314-787X

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