resorting to this new label. Only if the question of withdrawing active treatment arises is it necessary to consider how to define the boundaries, and at present there are no legal implications associated with this part of the awareness spectrum. In summary, doctors should avoid using this label in daily clinical practice, and it should be reserved for research (and possibly legal) practice.

DTW assesses patients in the vegetative state to provide the legal system with expert advice.

Derick T Wade
Oxford Centre for Enablement, Windmill Road, Oxford OX3 7LD, UK
(e-mail: derick.wade@dial.pipex.com)

1 Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002; **58:** 349–53.
2 Wade DT, Johnson C. The permanent vegetative state: practical guidance on diagnosis and management. *BMJ* 1999; **319:** 841–44.

Fear the pain

Patients fear pain mainly because of its aversive character. In experimental animals a single strongly painful stimulus can induce fear-conditioning that lasts for the animal's lifespan. Neither patients nor many doctors fear, however, the long-term consequences that can arise if pain is not adequately treated. But this nonchalance is not well justified, as trauma, inflammation, and nerve injury can not only evoke strong acute pain sensations but can also sensitise the peripheral and/or the central nociceptive system for prolonged periods.[1] This sensitisation can result in enhanced sensitivity to painful stimuli (hyperalgesia) and in pain that is evoked by normally non-painful stimulation (allodynia).[2] Strong painful stimuli produce excessive excitation in the spinal dorsal horn, which in turn potentiates transmission at glutamatergic synapses between nociceptive nerve fibres and neurons in the spinal dorsal horn.[3] Thus, pain itself is a risk factor for sensitisation and pain chronicity. To prevent the activity-dependent synaptic long-term potentiation it is essential to intervene at early steps of the signal-transduction cascade so that excessive excitation in the spinal cord is avoided.

In the clinical context effective pre-emptive analgesia can consist of regional anaesthesia and/or analgesia with opioids.[4] General anaesthesia with volatile anaesthetics is, however, ineffective. The signal-transduction pathways that result in sensitisation in the spinal cord involve a rise in free cytosolic calcium in nociceptive dorsal horn neurons and activation of calcium-dependent enzymes that directly or via modification of gene transcription enhance synaptic transmission. This enhanced transmission may be due to an array of synaptic modifications, including an increase in the number of postsynaptic neurotransmitter receptors and potentiation of receptor function.[5] For example, at glutamatergic synapses of nociceptive nerve fibres, phosphorylation of ionotropic glutamate AMPA-type (alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic-acid) receptors enhances their mean open-time and single-channel conductance on receptor binding. Phosphorylation of the NMDA (N-methyl-D-aspartate) type of glutamate receptors removes the voltage-dependent magnesium block. These phosphorylations synergistically result in increased synaptic strength.[6] At present little is known about how to reverse long-term potentiation at nociceptive synapses—ie, how to erase memory traces of pain. Most likely, intervention at the latest stages of the signal-transduction pathway will be succcessful. Dephosphorylation of glutamate-gated ion channels could restore normal synaptic function and normal pain sensitivity.

Results from previous studies suggest that memory traces in pain pathways occur by similar if not identical molecular and cellular mechanisms as those involved in cognitive and emotional learning.[3] Long-term potentiation was first identified at synapses in the hippocampus and later at other brain sites including the amgydala—ie, in areas that are implicated in cognition and emotion such as fear conditioning.[6] Synaptic long-term potentiation is now considered a major cellular model of learning and memory formation.[7] Thus prevention and reversal of long-term potentiation in nociceptive pathways may inevitably also impair higher brain functions. For example, activation of cannabinoid receptor 1 may not only attenuate hyperalgesia and allodynia[8] but also facilitate extinction of fear-conditioning induced by noxious foot-shock.[9]

A recent study by F Wei and colleagues[10] now provides the first direct evidence that signal-transduction pathways for pain-induced sensitisation may at some stage diverge from those of pain-induced fear-conditioning. The investigators measured three different effects that can be evoked by strong noxious stimuli in animals: acute pain responses, hyperalgesia and allodynia, and fear-conditioning. They used mice that were genetically manipulated such that the gene that encodes for calcium-calmodulin-dependent protein kinase IV (CaMKIV) was either deleted (*CaMKIV-/-*) or intact (wild type). CaMKIV activates by phosphorylating the transcription factor cyclic AMP-responsive element binding protein (CREB) that is centrally involved in the formation of long-term memory.[11] *CaMKIV-/-* mice showed acute pain responses, hyperalgesia, and allodynia that were indistinguishable from wild-type mice. Fear-conditioning was, however, impaired in *CaMKIV-/-* mice, indicating that activation of CREB via CaMKIV is not necessary for normal and potentiated responses to painful stimuli but is required for full expression of cognitive memory related to a noxious stimulus.[10] This finding raises possibilities for future work to identify selective targets to obliterate memory traces of pain.

JS is supported by Deutsche Forschungsgemeinschaft, Germany, Fond zur Förderung der Wissenschaftlichen Forschung, Austria, and by intramural funds of Heidelberg University, Germany, and Vienna University, Austria.

Jürgen Sandkühler
Brain Research Institute, Vienna University Medical School, A-1090 Vienna, Austria
(e-mail: juergen.sandkuehler@univie.ac.at)

1 Jensen TS, Gottrup H, Kasch H, Nikolajsen L, Terkelsen AJ, Witting N. Has basic research contributed to chronic pain treatment? *Acta Anaesthesiol Scand* 2001; **45:** 1128–35.
2 Sarkar S, Aziz Q, Woolf CJ, Hobson AR, Thompson DG. Contribution of central sensitisation to the development of non-cardiac chest pain. *Lancet* 2000; **356:** 1154–59.
3 Sandkühler J. Learning and memory in pain pathways. *Pain* 2000; **88:** 113–18.
4 Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. *Lancet* 1993; **342:** 73–75.
5 Willis WD. Role of neurotransmitters in sensitization of pain responses. *Ann N Y Acad Sci* 2001; **933:** 142–56.
6 Schafe GE, Nader K, Blair HT, LeDoux JE. Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. *Trends Neurosci* 2001; **24:** 540–46.
7 Malenka RC, Nicoll RA. Long-term potentiation—a decade of progress? *Science* 1999; **285:** 1870–74.
8 Bridges D, Rice AS, Rice AS. The synthetic cannabinoid WIN55,212-2 attenuates hyperalgesia and allodynia in a rat model of neuropathic pain. *Br J Pharmacol* 2002; **133:** 586–94.
9 Marsicano G, Wotjak CT, Azad SC, et al. The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 2002; **418:** 530–34.
10 Wei F, Qiu CS, Liauw J, et al. Calcium calmodulin-dependent protein kinase IV is required for fear memory. *Nat Neurosci* 2002; **5:** 573–79.
11 Deisseroth K, Bito H, Tsien RW. Signaling from synapse to nucleus: postsynaptic CREB phosphorylation during multiple forms of hippocampal synaptic plasticity. *Neuron* 1996; **16:** 89–101.