Pain assessment and management in disorders of consciousness

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Purpose of review

Pain and suffering controversies in persons with disorders of consciousness continue to be debated by the scientific, legal and medical ethics communities. This review examines the current knowledge base for guiding decisions regarding assessment and management of pain in persons with disorders of consciousness.

Recent findings

Studies have shown that brain processing linked to pain in persons in a vegetative state is incomplete and is processed only at a primary and not higher secondary level. Therefore, such painful stimuli would not reach the threshold for conscious experience. In contrast, persons in a minimally conscious state have been shown to have brain activation patterns to pain similar to controls. Therefore, these patients may have sufficient cortical integration and access to afferent information to allow for nociceptive stimuli to be consciously processed. Data to date do not allow for differentiation of the degree of any conscious pain experience or determination of whether individuals with disorders of consciousness are able to suffer.

Summary

Pain and suffering should be considered in all persons with disorders of consciousness and adequately treated. Behavioural assessment scales developed for patients unable to speak could be used to assess pain. Future studies should focus on methodologies for specific pain measures relevant to this unique and challenging patient population.

Keywords

analgesic, behavioural scale, consciousness, pain, suffering

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Abbreviations

DOC disorder of consciousness
MCS minimally conscious state

1350-7540

Introduction

Progress in acute neurocritical care has led to an increase in the number of patients surviving severe brain injury. Additionally, as a greater level of scrutiny has evolved regarding the historical limitations of our abilities to assess awareness of persons with disorders of consciousness (DOCs) (i.e. coma, vegetative state and minimally conscious state – MCS) via bedside examination, there has also been a concurrent introspection driven by clinical, medicolegal and ethical concerns regarding whether such individuals feel pain or suffer. In this article we will discuss the definition of pain, neural correlates of pain, remnant brain activity linked to pain perception in DOCs, with particular focus on vegetative state and MCS, assessment of pain perception in DOCs, management of pain in DOCs, and ethical questions linked to pain treatment in DOCs.

Definition of pain

Pain is defined as an unpleasant sensory and emotional experience associated with real or potential tissue damage. Pain experience is therefore mainly a subjective experience mediated in part by beliefs or emotions [1]. Acute and chronic pain must be distinguished from each other. Indeed, chronic pain typically is associated not only with a higher incidence of psychological concomitants but also central sensitization [2–4]. In this review, we will be more focused on mechanisms of acute pain given the more identifiable neuroanatomic pathways. Furthermore, only acute pain has been investigated, to date, in vegetative state and MCS.

Neural correlates of pain

At present, our understanding of the neural correlates of pain and suffering remain incomplete. The neural correlates of acute pain involve the lateral and medial pain systems. The lateral pain system includes the lateral thalamus, primary and secondary somatosensory cortex (SI and SII), parietal operculum and insula. The medial pain system involves the medial thalamus, anterior cingulate cortex, amygdala, hippocampus, hypothalamus, locus coeruleus, and periaqueductal grey matter. The

pain neuromatrix is composed of other structures, including the primary motor cortex, supplementary motor area, cerebellum and frontal cortex [5••–7••].

Pain, therefore, is mediated by a widely distributed cerebral neural network. A distinction must be made between brain areas involved in pain perception *per se* versus suffering as related to the conscious perception of the pain in question. Activation of the lateral thalamus, the primary and secondary somatosensory cortex, and the insula are related to the sensory-discriminative aspects of pain [8••] processing, whereas bilateral thalamic responses are related to generalized arousal following noxious stimulus. The descending connections of the anterior cingulate cortex to the medial thalamic nuclei and to the periaqueductal matter are thought to be involved in the modulation of reflex responses to noxious stimuli, whereas the cingulate, orbitofrontal and medial prefrontal cortices are thought to be involved with pain-related affective behaviour. Additionally, a recent study showed that activity in the anterior cingulate cortex and insula just before pain stimulation can increase pain perception [9••]. Moreover, interconnectivity between the periaqueductal matter and orbitofrontal cortex may be key to cognitive-emotional responses associated with pain. Thus, the central pain control processes seem to concern the cognitive-evaluative, motivational-affective, and sensory-discriminative systems that characterize the pain response [10••].

There is still some debate regarding whether conscious perception of pain may be mediated by subcortical centres. Evidence for such speculation comes from children with hydranencephaly [11]. Despite total or near-total absence of functional cortex, these children have been shown to be discriminatively aware. They can distinguish people and environments and are capable of social interaction, visual orientation, musical preferences, appropriate affective responses, as well as associative learning [12]. A subcortical system comprising the basal ganglia, medial and midline thalamic nuclei, substantia nigra, ventral tegmental area, superior colliculi, midbrain, and pontine reticular formation has been theorized by Merker [13••] to mediate the organization of consciousness. That intact forebrain commissures are not required for higher levels of cognitive functioning provides further evidence for the subcortical integration of both cerebral hemispheres, symmetrically and radially connected to this midline system. Multiple lines of evidence thus corroborate that the key mechanisms of conscious sensory perception are not dependent on cortical activity *per se*. Consistent with this evidence, the responses to noxious stimulation of children with hydranencephaly are purposeful and similar to those of intact children. Further, preterm neonates or adolescents with cortical parenchymal injury mount biobehavioural responses to pain that are indistinguishable from those of normal controls [14]. At present, however, the vast majority of neuroscientific evidence points to the critical role of thalamo-cortical interactions subserving conscious experience [15]. The question of whether consciousness is required for sensory perception, including pain perception and suffering in persons with DOC, has certainly been posited, particularly as related to the vegetative state [12,16].

Pain and altered states of consciousness

Recently, Laureys *et al.* [17] investigated central processing of pain stimuli by using PET. Electrical stimulations of the median nerve were administered to 15 patients in a vegetative state and changes in regional cerebral blood flow were compared with 15 healthy controls. Noxious stimulation activated midbrain, contralateral thalamus, and primary somatosensory cortex in each and every vegetative patient. Moreover, the activated primary somatosensory cortex was functionally disconnected from secondary somatosensory, bilateral posterior parietal, premotor, polysensory superior temporal, and prefrontal cortices. Primary cortex activation seems to be isolated from higher-order associative cortical activity [17]. These results were replicated by Kassubeck *et al.* [18] with seven anoxic patients in a vegetative state. Hypermetabolism was found in the posterior insula/secondary somatosensory cortex, postcentral gyrus/primary somatosensory cortex, and the cingulate cortex contralateral to the stimulus and in the posterior insula ipsilateral to the stimulus. Note that if activation in the anterior cingulate cortex is taken as a marker of affective perception of pain, the Kassubeck data could be interpreted as evidence that vegetative state patients show some residual perception. Brain processing, however, is too incomplete to suggest conscious perception.

Considering the controversy of subcortical pain perception, only some parcellar areas such as the thalamus and the midbrain appear to be activated in vegetative state patients upon nociceptive stimulation. Furthermore, functional disconnections in cortico–thalamo–cortical (between thalamus and frontal cortex) pathways have been identified via functional brain imaging, suggesting that cortical processes in the vegetative state may occur as a primary, isolated and disconnected processing phenomenon [19•,20]. Therefore, such painful stimuli would not reach the threshold to become consciously experienced.

In contrast with the limited brain activation found in vegetative state patients, Boly *et al.* [21] showed brain activation similar to controls (involving the anterior cingulate area which is known to be linked to pain unpleasantness) in response to noxious stimuli in a patient in a MCS. These data suggest that MCS patients

may have sufficient cortical integration and access to afferent information to allow for awareness of nociceptive stimuli. One cannot necessarily generalize these limited data to all MCS patients, however, as it may be possible to have awareness of certain phenomena and not pain, and vice versa. The aforementioned research finding also does not address the question of the degree of normalcy of pain perception or the presence of suffering potential in patients in a MCS. Specifically, pain perception must be differentiated from suffering, as the latter involves a complex cognitive-affective phenomenon involving not only a negative emotional response to the pain experience but also the ability to remember that particular experience or set of experiences. Future research should address methodologies to assess not only the ability to perceive pain, but also the degree of normalcy of the pain perception, as well as its association with any suffering.

Pain assessment in disorders of consciousness

Pain is a subjective experience. Patients with DOCs cannot generally provide a self-report of pain. Components of emotion that are relevant to pain experience, however, include behaviours such as facial expressions and body language associated with pain, affective reactions to pain including anxiety (or pain anticipation) or autonomic arousal associated with bodily reactions to pain [22]. The main way to detect conscious perception in DOC patients is based on serial bedside neurobehavioural assessment. Clinicians assessing awareness in patients with DOC administer various language, auditory, visual, somatosensory, as well as noxious stimuli in order to judge whether the patient's responses are indicative of conscious perception or merely suggest reflexive activity. Usually, three types of motor responses to pain are considered following application of a noxious stimulus: stereotypical responses (i.e. slow stereotyped flexion or extension of the upper and lower extremities), flexion withdrawal and localization responses. These responses are respectively linked, based on current understanding and theory, to brainstem, subcortical or cortical activity, respectively [23]. Localization of pain is the only motor response considered indicative of conscious perception [24], but without specificity of the degree of pain or its saliency to the person. Pain localization does not necessarily imply that the patient suffers as a consequence of either the nociceptive stimulus or pain in general, but this possibility has to be considered. Grimaces or cries, unless shown to be linked to specific environmental triggers, are generally not considered to be indicative of awareness, as they can occur reflexively through subcortical pathways in the thalamus and limbic system. Vegetative patients can, however, demonstrate responses such as grimaces, diaphoresis, tachycardia, tachypnoea and posturing, causing them to often be misdiagnosed as perceiving pain, when they would traditionally be deemed, inherent in their vegetative state diagnosis, to not be able to consciously perceive pain or suffer [25].

The detection of awareness is difficult in DOC patients. Indeed, for motor impairment, vigilance fluctuation, and the inherent challenges of bedside evaluation, studies have shown a high misdiagnosis rate (i.e. around 40% of MCS patients are misdiagnosed as being in a vegetative state) [26•]. A recent study involving a patient who met criteria for vegetative state underwent functional brain imaging and showed distinct evidence of higher level brain processing in response to verbal instruction (i.e. mental imagery tasks [27]). This patient subsequently emerged in a MCS a short time after the experiment [28•].

Standardized behavioural tools are therefore recommended to decrease the probability of missing signs of conscious perception [26•]. All these evaluative scales, however, do not assess responses to pain (Table 1) [29–32]. The techniques used to detect conscious pain perception, therefore, vary according to the behavioural scale. These behavioural scales have been shown, however, to have different levels of sensitivity. Recently, Schnakers *et al.* [33•] observed that of 29 patients considered as being in a vegetative state based on the Glasgow Coma Scale, the Full Outline of UnResponsiveness (FOUR) [31] identified four of them as being in a MCS, whereas, the Coma Recovery Scale-Revised (CRS-R) [30] identified an additional seven patients as meeting criteria for MCS set forth by the Aspen Workgroup. The CRS-R, therefore, seems to be the most sensitive DOC assessment measure for detection of conscious perception. The CRS-R scale, however, is only adapted to detect signs of awareness, not monitor pain or suffering. In fact, there currently exists no behavioural scale adapted to assess pain in DOCs.

Behavioural scales to assess pain in noncommunicative patients such as elders with advanced dementia, infants or intubated/sedated patients have already been developed and validated (Table 2) [34••,35–43]. These scales take into account the motor, verbal, facial and physiological responses associated with acute pain and could therefore potentially be examined, likely with modifications, for use in persons with DOCs.

Pain responses should be routinely monitored with a concurrent understanding of the neurobehavioural and neurological status of the patient in question. Appropriate use of scales designed specifically for persons with DOCs should be used in conjunction with documentation of the nature, consistency, and temporal lag (if any) of pain responses in an attempt to facilitate appropriate pain

Table 1 Selection of behavioural scales with assessment of pain response

Scale name	Reference	Pain assessment
Glasgow Coma Scale (GCS)	Teasdale and Jennett [29]	Three components: eye (E), verbal (V) and motor (M) response to external stimuli Procedure: as regards to motor responses, pressure is applied to the fingernail bed with a pencil, resulting in either flexion or extension at the elbow. If flexion is observed stimulation is then applied to the head and neck and to the trunk to test for localization Number of stimulations: not explicitly mentioned Quotation: best response observed
Coma Recovery Scale-Revised (CRS-R)	Giacino *et al.* [32]	Basic structure is similar to the GCS. It includes similar visual, motor and verbal subscales but there are in addition three other scales: an auditory function scale, a communication scale and an arousal scale Procedure: a deep pressure applied to the nail beds of each extremity to detect stereotypical responses (flexion and extension are undifferentiated), flexion withdrawal or localization to noxious stimulation Number of stimulations: two times each side Quotation: considered as present if behavior observed two out of four times
Full Outline of Un Responsiveness (FOUR)	Wolf *et al.* [31]	Scale consists of four components (eye, motor, brainstem, and respiration) with a maximal score of 4. In this scale, the motor component combines decorticate and withdrawal flexion responses (the authors consider that the distinction is difficult to appreciate) Procedure: the painful stimulus is applied to the temporomandibular joint or supraorbital nerve Number of stimulations: not explicitly mentioned Quotation: best response to the stimulation
Coma/Near-Coma Scale (CNC)	Rappaport *et al.* [35]	Mainly assesses responses to auditory, visual, verbal, tactile, olfactory, threat and noxious stimulation Procedure: two stimuli are used to assess response to pain: firm pinch on finger tip; robust ear pinch/pull Number of stimulations: three times each side Quotation: score of 0–4 according to the number and the type of response observed

management strategies, as well as communication among the treating medical staff.

Pain treatment in disorders of consciousness

This section examines medical considerations, pharmacological management and ethical considerations of treating pain in DOCs.

Medical considerations

In the acute care setting, already compromised neurological status may limit the array of pharmacotherapeutic agents appropriate to use in a patient whose status is neither stabilized nor static. Medications that potentially alter any aspect of the neurological assessment should be used with caution in the acute care setting in persons with DOCs. Additionally, consideration should be given to medications with reversible effects (e.g. opiate reversal with naltrexone) whenever there is question of medication effect versus ongoing deterioration of neurological status.

During the acute care phase, the primary pain generators in trauma patients will be fractures, intraabdominal injuries, soft tissue injuries and pain associated with

Table 2 Selection of behavioural scales which assess acute pain in noncommunicative patients

Population	Behavioural scale	Reference
Advanced dementia	ADD: The Assessment of Discomfort in Dementia Protocol	Kovach [35]
	CNPI: Checklist of Nonverbal Pain Indicators	Jones [36]
Infants and preverbal toddlers	COMFORT Behavior Scale	van Dijk [37]
	PIPP: Premature Infant Pain Profile	Stevens [38]
	CRIES	Krechel [39]
	CHIPPS	Buttner [40]
	CHEOPS: Children's Hospital of Eastern Ontario Pain Scale	McGrath [41]
	FLACC: Faces, Legs, Activity, Cry, Consolability Observational Tool	Willis [42]
Intubated/sedated patients	BPS: Behavioral Pain Scale	Payen [43]

Data from Ref. [34••].

invasive procedures. For neurologically compromised patients with response limitations, such as would be seen in persons with DOCs, prophylactic pain management should be practised based upon injuries sustained and clinical presentation. Pharmacologic prophylaxis of pain should be considered in persons with DOCs given, firstly, the difficulty in assessment of pain in this patient subgroup, as well as controversies regarding pain appreciation and suffering in patients whose awareness of pain may be difficult, if not impossible, to confirm; and secondly, the negative impact of pain (even in patients in a vegetative state) related to subcortical physiologic responses to nociceptive stimuli (or, for that matter, any physiological stressor), including increased tone/posturing, tachycardia, tachypnea, diaphoresis in addition to other adverse effects.

In the subacute setting, many of the same issues present in the acute care setting will continue to serve as pain generators. As patients are weaned from pain medication, pain severity can increase and acute pain generators can evolve into subacute pain generators. Ongoing attention to pain management must be continued as patients are moved to neurosurgical step-down units or inpatient rehabilitation units.

Chronic pain has many elements of acute and subacute pain but is generally promulgated by additional factors, including psychological ones. Current evidence strongly supports mechanisms of central sensitization in chronic pain phenomena which are not present in the acute and subacute periods. The patient suffering from chronic pain should be treated just as aggressively as a patient with acute or subacute pain, but because peripheral pain triggers are frequently less obvious, generally with different/additional modalities.

Pain may affect functional assessment in persons with DOCs and must be adequately assessed and treated. Pain in persons with DOCs may be due to spasticity, contracture, fractures, pressure sores, soft tissue ischaemia, peripheral nerve injuries, complex regional pain syndrome, central pain syndromes (e.g. thalamic pain) and postsurgical incisional pain, among numerous possibilities. Appropriate pain management starts with identifying the specific pain generator(s) and not just treating the symptom of pain unless a source cannot be found. Acquisition of an adequate pain history is critical in order for the clinician to provide an adequate foundation for identifying possible or probable pain generators. In persons with DOCs, such a history would likely come from the extant file and persons who have worked with the patient, including potentially significant others/family. Clinicians are cautioned against assumptions that commonly reported posttraumatic pain symptoms are due to the brain injury itself (e.g. posttraumatic headache) when pain is more commonly produced by extracerebral injury. Evaluating clinicians should be familiar with both the broad array of pain symptoms that may be reported by posttrauma patients, as well as assessment methodologies for the various types of pain seen in this population.

Pharmacological management

Mild pain medicines that should be considered typically include aspirin, acetaminophen and NSAIDs. For moderate pain the following may be considered: high-dose aspirin or acetaminophen, oral NSAIDs, newer generation NSAIDs such as cyclooxygenase II inhibitors (now limited to the single agent, celecoxib), injectable NSAIDs (such as ketorolac), mixed opiate analgesics with aspirin or acetaminophen (with or without caffeine) and tramadol. For severe pain, medications to consider would include parenteral opiates (morphine sulfate = standard), mixed agonists/antagonists (pentazocine, nalbuphine), partial agonist opiates (buprenorphine), antidepressants, anticonvulsants, and atypical agents. Stimulants such as methylphenidate are used with opioid analgesics as an adjuvant analgesic and to help manage opioid-induced sedation and cognitive impairment.

Nerve damage with both peripheral and central pain generators is not uncommon in posttrauma patients. Some posttrauma patients may present with both opioid-sensitive and opioid-insensitive pain at different sites and due to different aetiologies. Medications that have been used for opioid insensitive pain include NSAIDs, tricyclic antidepressants, newer generation antidepressant agents such as venlafaxine or duloxetine, tizanidine, antiepileptic medications, and various topical medications (some of which may need to be produced through compounding pharmacies), among other pharmacotherapeutic options [10••].

Ethical considerations

Providing empathic and compassionate care to individuals who cannot report their pain is directed by the ethical principles of beneficence and nonmaleficence. These principles oblige medical staff to provide pain treatment and comfort to all patients, even challenging noncommunicative individuals [34••]. It is our opinion, based on both extensive clinical experience and recent data questioning the ability of the bedside exam, even when sophisticated, to delineate awareness in at least some patients with DOCs, that one is likely taking the safer course by treating all DOC patients as if they had the potential to perceive pain and suffer. This does not mean that all patients with DOCs do suffer but if we are at a minimum doing 'no harm' as per our Hippocratic oath commitments, then we should at least take the course of palliating pain in this special population of neurological patients.

With regards to persons in a MCS, brain activity seems similar to controls with regards to the neural substrates for pain perception and suffering [21]. Therefore, such data suggest treating patients in a MCS regardless of the details of their clinical exam. Data concerning patients in a vegetative state, however, have shown brain activity involving primary, albeit 'functionally disconnected' from secondary, cortical areas. These latter results suggest the absence of an integrated pain perception system in persons in a vegetative state.

Regardless of the aforementioned, the ultimate clinical question is really different from the often asked medicolegal question regarding pain and suffering in DOCs; that is, clinically, we want to be certain that an individual is not in pain or suffering when making clinical decisions about treatment, whereas in a medicolegal context, all we are asked is whether a determination with a degree of medical probability can be made regarding whether or not that individual can perceive pain or suffer. As pain is a subjective experience that is modulated by numerous factors, including affective status, cultural background, level of awareness, degree of arousal and intactness of memory functions, among others, we can, at least currently, never be totally sure what patients with DOCs 'feel' and to what degree, if any, they may suffer. Considering the levels of clinical uncertainty, pain treatment should be considered in all patients in a vegetative state or MCS.

Conclusion

Pain and suffering should be considered in all persons with DOCs. Behavioural assessment scales developed for patients unable to speak due to DOC could be used to assess pain; however, future studies should focus on methodologies for specific pain measures relevant to this patient population. Clinicians should be familiar with assessment strategies for pain in persons with DOCs and the differential work-up of 'pain behaviour' in this group of catastrophically impaired patients relative to the myriad potential sources of pain following the types of insults that result in states of DOCs. Additionally, as clinicians, we should be familiar with hierarchical pain treatment options for persons in states of DOCs, including pharmacological management. Note that current practice is different as regards to current standards in artificial nutrition and hydration withdrawal in vegetative state patients when no opioids are given [44]. Ultimately, researchers should focus on the neuroimaging and neurophysiological correlates of pain and suffering in persons with DOCs to allow us to advance beyond empiricism as far as how such patients are assessed and treated relative to pain and suffering. Lastly, further research is warranted on issues of assessing acute versus chronic pain presentations and treatment in persons with DOCs.

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