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ESSENTIALS AND BASICS

Pain Management in Neurocritical Care

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Abstract The core challenge of pain management in neurocritical care is to keep the patient comfortable without masking or overlooking any neurological deterioration. Clearly in patients with a neurological problem there is a conflict of clinical judgement and adequate pain relief. Here we review the presentation, assessment, and development of pain in the clinical spectrum of patients with associated neurological problems seen in a general intensive care setting. Many conditions predispose to the development of chronic pain. There is evidence that swift and targeted pain management may improve the outcome. Importantly pain management is multidisciplinary. The available non-invasive, pharmacological, and invasive treatment strategies are discussed.

Keywords Intensive care · Pain · Analgesia · Neurocritical care

Introduction

From a patient's point of view, pain is probably the most frequent symptom experienced in the intensive care unit (ICU). Moderate to severe pain occurs in up to 63 % of surgical patients [1]; it is a major stress factor [2, 3] and many patients recall significant pain for a long time after being discharged from the ICU [4–6]. Recognizing and systematically recording pain in an ICU considerably improves patient care through improved patient management [7, 8].

Pain is omnipresent and in many of the diseases reviewed here (see Table 1) both pain *perception* and pain *expression* are impaired. Altered pain *perception* is caused by pathology of the nociceptive pathways or the influence of other modalities (sensory, autonomic, affective). Importantly, patients frequently cannot *express* their pain because of impairment of the language, motor, cognitive, and behavioral systems. This increases stress, agitation, and anxiety in patients, with considerable impact on nursing care [9].

Recognition and documentation of pain in the neurocritical care patient is not straightforward because of altered consciousness. The recognition of pain is predominantly based on indirect evidence from physiological parameters following sympathetic activation. Bed-side signs include widened pupils, sweating, increased heart rate, and blood pressure. Extending on the bed-side assessment increased sympathetic activity can be objectivated by electrodermal activity, electromyographic activity, and cortical evoked potentials. Validated *behavioral physiological* scales (Table 2) add to this information [8, 10–12]. The terminology used to describe pain in this review is summarised in Table 3. Pragmatically, pain is either iatrogenic or caused by the underlying disease.

Iatrogenic Pain

On the ICU, patients are routinely exposed to painful stimuli [13, 14]. For a long time afterwards about 90 % of patients recall many of these as unpleasant or stress-evoking [2]. On a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst pain ever) [15], endotracheal

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Table 1 An alphabetical list of the spectrum of diseases encountered with pain in neurocritical care

Disease	Pain			Likelihood for chronic pain
	Neurogenic	Neuropathic	Central	
Anterior spinal artery infarct (ASAS)	+	+++	+++	+
Ateriovenous malformation (AVM)	+	+	+	+
Behçet's syndrome (BS)	?	—	—	+
Eclampsia	+	+	—	
Encephalopathies	?	?	+	
Encephalitis	+	+	+	+
Epileptic syndromes	—	+	+	+
Guillain–Barré syndrome (GBS)	—	+	—	+
Headache syndromes	+++	+++	+	+++
Meningitis	+	+	—	—
Multiple sclerosis (MS)	+	+++	+++	+++
Myasthenia gravis (MG)[a]	+++	—	—	+++
POEMS syndrome	+++	+	—	?
Post-operative	+++	+++	+	+
Paraneoplastic disease	+	+	?	+
Poliomyelitis	+	+++	+	+++
Prion disease	?	?	+	?
Root avulsion	+++	+++	—	+++
Sinus venous thrombosis (SVT)	+	+	—	—
Spinal cord injury (SCI)	+++	+++	+++	+++
Subarachnoid hemorrhage (SAH)	+++	+++	—	+
Stroke	+	+	+	+
Syringomyelia	+	+++	+	+++
Tetanus	+++	?	?	—
Traumatic brain injury (TBI)	+++	+++	+	+
Tumor	+	+	+	+
Vasculitis	+	+++	+	+++

The likelihood for the presence of neurogenic, neuropathic, and the development of chronic pain is rated with; likely = +++, possible = +, unlikely = —. A question mark (?) indicates that there is insufficient published evidence to allow for any estimate, but that such an association would not be surprising for anatomical or pathophysiological reasons

[a] Post thymectomy

suctioning is rated 4.9 and the removal of a chest tube scores 6.6 [16]. For comparison, giving birth is rated at about 4.5 [17]. Iatrogenic pain (Table 4) and pain following surgery (Table 5) can be anticipated and reduced by targeted analgesia (Table 6).

Pain Specific to Neurocritical Care

Neurogenic, neuropathic, and central pain are big problems in neurocritical care (Table 1). Of these, central pain is of particular relevance to the neurocritical care physician and difficult to manage. Central pain is most severe when lesions affect the spinal cord, lower brainstem and ventroposterior part of the thalamus [18–20]. The most common causes of central pain seen in neurocritical care are summarised in Table 7. Immediate pain relief is achieved by short-term analgesia (Table 8). The clinical features and management of this pain are discussed further down.

Pain Management and Consciousness

There is considerable and justified fear within the general medical community that aggressive pain management clouds the level of consciousness and, therefore, masks any neurological deterioration [21]. Ultra short-acting drugs given on a scheduled basis allow accessing levels of consciousness and pain at regular intervals.

Pain Management Improves Outcome

Chanques et al. [7] reported that closely monitored pain and targeted analgesia reduced the duration of mechanical

Table 2 The behavioral pain score [12]

Term	Score	Description
Facial expression	1	Relaxed
	2	Partially tightened (e.g., brow lowering)
	3	Fully tightened (e.g., eye lid closing)
	4	Grimacing
Upper limbs	1	No movement
	2	Partially bent
	3	Fully bent with finger flexion
	4	Permanently retracted
Compliance with ventilation	1	Tolerating movement
	2	Coughing but tolerating ventilation for most of the time
	3	Fighting ventilator
	4	Unable to control ventilation

ventilation and number of nosocomial infections. A possible biological basis for this is that analgesia reduces the stress response (i.e., tachycardia, myocardial and systemic energy consumption, hypercoagulability and immunosuppression) [22]. More specifically, analgesia may reduce pulmonary complications by preventing generalized muscle rigidity due to pain which could restrict chest wall and diaphragmatic movements [23, 24] and unplanned extubation. Finally, adequate analgesia reduces overall agitation and delirium. Particularly reduction of delirium is of importance because delirium prolongs ICU stay and overall time of hospitalization.

Guidelines Reduce the Financial Burden

The costs of ICU care are considerable, and reached $81 billion in the USA in 1997, with sedative drugs taking a 10–15 % toll on total drug expenditure. The mean daily costs for narcotics decreased by about 75 % (from USD 28.28 to USD 6.94) when specific guidelines were followed [25]. A detailed breakdown of the money spend on sedatives shows for cost reduction by 63.5 % (from USD 533.99 to USD 194.52) for propofol and benzodiazepines, a 89 % cost reduction for neuromuscular junction blocker (from USD 441.17 to USD 45.88). Unfortunately, the added costs for a likely increased used of analgesics (morphine, meperidine, fentanyl) were not published [25]. Robust and unbiased pharmacoeconomic studies on cost reduction for analgesic-based sedation are complex because the key lies in avoidance of drug-related adverse events which may contribute to prolonged ICU stay [26]. Overall adherence to guidelines consistently demonstrated improved outcome and cost reduction (see Refs. 138–152 in [26]).

Table 3 Definition of terms used in the description of pain

Term	Definition
Allodynia	Pain due to a stimulus which does not normally provoke pain
Analgesia	The absence of pain in response to stimulation which would normally be painful
Central pain	Pain initiated or caused by a primary lesion or dysfunction in the central nervous system
Hyperalgesia	An increased response to a stimulus which is normally painful
Hypoesthesia	Decreased sensitivity to stimulation, excluding the special senses
Neuralgia	Pain in the distribution of a nerve or nerves
Neuritis	Inflammation of a nerve or nerves
Neurogenic pain	Pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system
Nociceptor	A receptor preferentially sensitive to a noxious stimulus
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
Pain threshold	The least experience of pain which a subject can recognize
Paresthesia	An abnormal sensation, whether spontaneous or evoked
Peripheral neurogenic pain	Pain initiated or caused by a primary lesion or dysfunction or transitory perturbation in the peripheral nervous system
Peripheral neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system

Adapted from the 1994 list of the IASP pain terminology (http://www.iasp-pain.org/terms-p.html)

The Spectrum of Neurological Conditions Associated with Pain seen in ICU

Pain is an important feature of a number of diseases seen in neurocritical care (Table 1). The clinical features and management of pain for each condition are reviewed. Where applicable, summary tables for pain management are presented.

Cerebrovascular Conditions

Ischemic strokes are the most frequent condition seen in neurocritical care and will, therefore, be discussed first. Second to ischemic stroke, SAH require specific pain management. Intracranial hemorrhages are only discussed in the context of aterio-vascular malformation because this poses a particular challenge for pain management as do the less frequently occurring ASAS. In addition to the arterial

Table 4 Common causes for iatrogenic pain, discomfort, and stress

Pain	Discomfort & stress
Arterial blood gas puncture	Inability to communicate
Arterial catheter insertion	Limits on visiting by loved ones
Central catheter insertion	Lights
Chest tube insertion	Noise
Chest tube removal	Odor
Endotracheal suction	Sleep disruption
Endotracheal intubation	Temperature of room
Indwelling urethral catheter	Ward rounds
Mechanical ventilation	Discussion around the bedside
Mobilization	
Moving from bed to chair	
Nasogastric tube insertion	
Nasogastric tube in place	
Peripheral iv insertion	
Turning in bed	

side, headaches due to a venous outflow problem need to be recognized. Finally inflammation of the cerebral vasculature is discussed.

Stroke

Central pain following stroke occurs in 1–35 % of patients [27–31]. Shoulder pain is even more frequently reported, ranging from 11 to 50 % [27, 32–34]. Compared to other medical complications following stroke, pain was the most frequent symptom during a 12-month follow-up (see Fig. 1 in Ref. [33]). Jönsson et al. [27] conducted a detailed population-based study on prevalence, intensity, and temporary evolution of pain in stroke patients. Importantly, the onset of pain was within 0–2 weeks following stroke in up to 31 % of patients. Moderate to severe pain was constant in 30 % and frequent in 68 % of all patients and interfered with sleeping in 49 %, four months after stroke [27].

Central pain is mostly due to a thalamic lesion, and Dejerine and Roussy [35] originally coined the term "syndrome thalamique" (thalamic syndrome). Central pain is excruciating and affects the contralateral body in about 75 % of patients [36]. Since the initial description of central pain following a thalamic insult, it became apparent that any lesion along the spino-thalamic pathway and its cortical projections can be the cause of central pain [37–42]. Therefore, some authors prefer to call this syndrome *central post-stroke pain* (CPSP) [43]. CPSP falls under the umbrella term of central pain (see Table 3). The differential diagnosis of central pain is summarised in Table 7.

Short-term treatment is possible (Table 8), but in the longer term pain management is very difficult and resistance to opioids is not uncommon [44]. Opioid resistance is probably caused by receptor desensitisation or opioid tolerance [45, 46]. Central pain may be triggered or intensified by any sensory input (i.e., cutaneous, visceral, auditory, visual) and mood [36, 47]. If recognized, the contribution of these factors can be limited. Drugs causing constipation should be avoided. Of note, morphine will always cause or contribute to constipation. Therefore, special attention should be paid to prevention of constipation by sufficient (enteral) water intake and laxatives. In a recent systematic review Frese et al. [44] summarised the results on treatment with antidepressants, membrane-

Table 5 Categories of pain to be expected following certain neurosurgical, or related, procedures

Severe pain	Moderate pain	Mild pain
Complex cervical, thoracic, lumbar spinal surgery	Craniotomy, cranioplasty	Increased intracranial pressure (ICP) bolt insertion
Cervical or lumbar laminectomy/laminoplasty	Posterior fossa craniectomy	Burr hole biopsy
Foramen magnum decompression[a]	Transsphenoidal hypophysectomy	Trigeminal thermocoagulation
Sacral nerve stimulator[b]	V/P shunt insertion and revision[c]	Drainage of a chronic subdural hematoma
	Anterior cervical decompression[d]	Carpal tunnel decompression
	Lumbar microdiscectomy	Ulnar nerve transposition[e]
	Spinal cord stimulator	Muscle biopsy
	Deep brain stimulator	
	Carotid endarterectomy	

Adapted from Ref. [282]

[a] Patients often have severe headache and nausea/vomiting post-op

[b] Patients often have severe nerve root nerve pain post-op

[c] Without infiltration of the abdominal wound with L.A. these patients are often in the "severe pain" category

[d] Patients with bone grafts usually need to be treated as in the "severe pain" category

[e] Patients having bone removed usually need to be treated as in the "moderate pain" category

Table 6 Management of severe, moderate, and mild pain in the post-surgical patient

Severe pain	Moderate pain	Mild pain
Regular analgesia for 48 h		
Paracetamol 1 g qds	Paracetamol 1 g qds	Consider Paracetamol 1 g qds
(Dihydrocodeine 30 mg qds)	(Dihydrocodeine 30 mgs qds)	Consider NSAIDs
Non-steroidal anti-inflammatory drugs (NSAIDs)	NSAIDs	(Consider dihydrocodeine 30 mg qds)
Consider laxatives[a]	Consider laxatives	
"As required" analgesia for 48 h		
Morphine s.c. patient-controlled analgesia (PCA)	Morphine s.c. PCA	Consider NSAIDs
Morphine i.m. 2 hourly	Morphine i.m. 2 hourly	(Consider dihydrocodeine 30 mg qds)
Remember anti-emetics	Consider Morphine i.m. 2 hourly	Remember anti-emetics

The use of bupivacaine at end of the procedure should be considered in all cases [278]. Adapted from Ref. [282]

[a] Can be introduced 12 h post-surgery if there had been no post-operative complication of hematological origin. There is no evidence to show that the earlier introduction of NSAIDs is dangerous. Indeed some neurosurgical centers use them immediately post-craniotomy if there are no problems with clotting. The vast majority of post-operative intra-cranial hemotoma develop in the first 6 h post-operatively [347]. The use of NSAIDs in patients with SAH must be avoided pre-angiography and in those cases where an aneurysm is detected and coiling or clipping considered. In angiogram negative SAHs and coiled/clipped aneurysms, the use of NSAIDs 12 h after the procedure can be discussed on a case to case basis

Table 7 The most frequent conditions leading to central pain

Aetiology	Approximate prevalence
Abscesses (brain, spinal cord)	n/a
Epilepsy	2.8 %
Iatrogenic (i.e., following chordotomy)	n/a
MS	28 %
Parkinson's disease	10 %
Syringomyelia and syringobulbia	n/a
TBI	n/a
Traumatic SCI	30 %
Tumors	n/a
Vascular lesions of the brain and spinal cord	8.4 %
Viral and syphilitic myelitis	n/a

Adapted from [36]

Table 8 Guidance for the short-term management of central pain (modified from Refs. [44, 50])

Drug	Route	Dose	Evidence	Reference
Lidocaine	IV	5 mg/kg over 5 min	Class III	[348–350]
Propofol	IV	0.3 mg/kg per hour	Class II/III	[351]
Amitriptyline	Oral	≥75 mg per day	Class II/III	[352]
Lamotrigine	Oral	≥200 mg per day	Class II/III	[330]
Mexiletine	Oral	≤10 mg/kg per day	Class III	[353]
Flovoxamin[a]	Oral	≤125 mg/kg per day	Class III	[354]
Gabapentin	Oral	≥1,200 mg per day	Class IV	[355, 356]
Motor cortex stimulation (MCS)	Transcranial	Repetitive	Class III	[54, 55]

[a] Only recommended if the stroke occurred less than one year ago

stabilizing drugs, glutamergic drugs, GABA-ergic drugs, and opioids (Table 8). Yet evidence on the efficacy of antiepileptic drugs on CPSP remains controversial [48]. Selective tumor necrosis factor inhibition may emerge as an alternative treatment option [49].

MCS and transcranial direct current stimulation (tDCS) may be interesting alternative future treatment strategies [50, 51]. MCS based on non-invasive transcranial magnetic stimulation has been shown to be effective by modulating pain perception centrally [36, 52, 53]. MCS was effective in 30–40 % of patients with central pain [54–56]. The effect of MCS on spinal cord or brainstem lesions may be less effective [54]. Recent evidence from a controlled trial suggests that tDCS may be of greater benefit than MCS in those patients with a mean point response of 58 % [51]. It will be interesting to learn from future studies if deep brain stimulation targeted at the nucleus accumbens may be open new avenues for the management of treatment resistant central pain [42].

Subarachnoid Hemorrhage (SAH)

A thunderclap headache is one of the cardinal presenting signs in SAH [57–59]. Because of the high mortality, SAH is one of the medical emergencies which must not be missed,

Table 9 Pain in secondary headache syndromes, classified according to the main underlying pathology

Vascular pathology	Metabolic or toxic	Intracranial pathology	Other causes
SAH	Pheochromocytoma	Intermittent hydrocephalus	Hypertensive encephalopathy
Unruptured aneurysm	Thyroid disease	Intracranial hypotension	Cervical spine disease
TIA	Drug induced	Tumor	Dental, ENT or ophthalmic disease
Stroke	Withdrawal syndrome	Arnold–Chiari malformations	Secondary to general medical conditions
Subdural hemorrhage	Hypercarbia		
Extradural hemorrhage			
Intracranial hemorrhage			
Dissection			
Cerebral venous thrombosis			
Vasculitis			

Adapted from Ref. [253]

and must be differentiated from a large list of other causes of secondary headaches (Table 9). The diagnosis is based on computed tomography brain imaging, cerebrospinal fluid analyses and angiography [60–62]. The severe headache in SAH is difficult to treat, and in our experience most patients continue suffering from headaches for quite some time following the bleed. The pathophysiology of this headache is not known and may be multifactorial. The use of codeine-containing painkillers may help with the headaches in the acute phase, but is associated with the risk of developing drug-induced chronic daily headaches if used prolonged.

The two main complications following successful protection of the aneurysm are vasospasm and hydrocephalus, both of which may become an additional cause of headaches, agitation, and confusion.

Most of the SAH patients suffer from severe pain; therefore, we recommend the use of regular oral paracetamol 1 g 6 hourly as outlined in Table 6. To further reduce discomfort resulting from photophobia and phonophobia airline eye covers and ear plugs are an option. If required, morphine PCA, as outlined above, with a maximum dose of 15 mg/4 h can be used. If the patient remains in pain and/or should be unsuitable for a PCA, we consider a small dose of i.m. morphine (approx. 0.1 mg/kg) or oral morphine (Sevredol/Oramorph at 0.2 mg/kg 3 hourly), to be increased as required. We consider it relevant that the patient is adequately monitored for maintaining hemodynamic function. Also the respiratory rate and the patient's ability to protect the airways should be closely monitored. Mechanical ventilation may be required in some patients. Close monitoring safeguards and likely also improves pharmacological management of pain.

Ateriovenous Malformations (AVM)

Vascular headache is an important but infrequent feature of brain AVM [63], occurring in about 11–14 % of patients [64–66], independent of age (see Fig. 1 in Ref. [66]). The most frequent presenting sign and reason for admission to a neurocritical care unit is an intracranial bleed. A cross-sectional study which prospectively enrolled all patients with an AVM seen at a single one-center between 1989 and 2003 ($n = 542$) found that an intracranial bleed was the presenting sign in 46 %, followed by a seizure in 29 % [66]. Because AVM pose a life-long risk for a bleeding some authors suggest obliterative treatment in all cases [67], but there is no international consensus [68] and a lack of randomised trial. The American Stroke Association published guidelines which recommend surgery for Spetzler–Martin grade I and II lesions, endovascular embolization for grade III lesions. Radiosurgery should be considered on a case to case basis. Treatment was not recommended for grade IV and V lesions because of the associated risks [69].

Central pain caused by AVMs poses a serious management problem because in the majority of cases central pain tends to remain after surgery. Table 8 outlines the short-term management of central pain in the neurocritical care unit. On the long term there are only few anecdotal reports of recovery from central pain [70] with the potential mechanisms of recovery remaining controversial [71].

Anterior Spinal Artery Infarct (ASAS)

The combination of sudden lanciating radicular pain together with sensory and motor symptoms is observed in the acute ASAS [72–76]. The most frequent presentation is back pain (82 %) [74, 77]. The initial differential diagnosis is not always straightforward [78–81] as chest pain has been mistaken for an acute myocardial infarct [82] and presenting headache is another, though much less common possibility [83, 84]. The initial pain in ASAS may become chronic in about a third of the survivors [85, 86]. There are no clear general treatment guidelines [76]. Because hypotension is an important cause, the first line management is focused on

cardio-vascular stabilization [74, 75]. Likewise there are no consensus guidelines on pain management. For the pharmacological management of acute pain in ASAS, Table 5 may be helpful. In patients with evidence for central pain the management may be extended as outlined in Table 8.

Sinus Venous Thrombosis (SVT)

Headaches are the most frequent (in about 80 %), one of the first, and occasionally the only, symptom in SVT [87, 88]. The onset of the headache can be progressive (65 %), acute (17.5 %) and thunderclap in nature (17.5 %). About 76 % of patients describe their headaches as severe and/or throbbing [87]. The pathophysiology of the headache is not clear and it may also occur in the absence of ICP. In those patients who do not survive, high ICP and tentorial herniation are the most frequent cause of death [89, 90]. The consensus guidelines advise anticoagulation with heparin in all patients with SVT in addition to ICP management and seizure control [91]. The guidelines also mention control of agitation and analgesia but no specific recommendations are made. We avoid the use of NSAIDs because of the effect on thrombocyte function and evidence that decompressive surgery [92] might be an option to prevent tentorial herniation [89, 90]. Likewise we do not give morphine because of potentially deleterious effects on ICP in other conditions where this is an important management issue [93].

For mild headaches (VAS $<$ 4/10) regular paracetamol can be sufficient. In patients with severe headaches this is likely due to high ICP and a therapeutic lumbar puncture (LP) can relieve symptoms. A multicenter study found this procedure to be safe in those 224 patients with SVT who underwent a LP [94].

Vasculitis

Collins and Periquet divided vasculitic neuropathies according to whether or not there was associated systemic disease [95]. Pain is a characteristic feature in periarteritis nodosa, Churg–Strauss syndrome, giant cell arteritis and Purpura–Schoenlein Hennoch, which is also occasionally seen in the adult patient [95, 96]. Pain is thought to be mainly related to ischemic injury. Immunosuppression halts the vasculitic process and abolishes pain in most patients almost instantly. Those patients with neuropathic pain on the background of a non-systemic vasculitic neuropathy may respond to gabapentin.

Trauma Related Conditions

Trauma is one of the main reasons for admission to the ICU. Of these we discuss pain management in TBI, followed by root avulsion and SCI. Because syringomyelia is also associated with traumatic aetiology it will be discussed here as well.

Traumatic Brain Injury (TBI)

Pain and agitation are a major management challenge in patients suffering from TBI. All patients require pain medication in the acute stage. About 24/35 (70 %) of patients with TBI following a road traffic accident still required narcotic medication for pain at time of discharge [97]. Nociceptive pain in TBI can result from damage to the cerebral and dural arteries, the dura mater and the trigeminal, glossopharyngeal, and vagus nerves. Important extracranial sources are skeletal muscle, tendons, joints, bone, viscera, skin and mucous membranes, deep fascia, periosteum, and peripheral nerves [98]. The most frequent causes of pain in TBI are summarised in Table 10. This list seems long, but Garland and Bailey remind us that about 11 % of fractures and 11 % of injuries to the peripheral nervous system remain undetected at the initial assessment [99]. Swift treatment of the primary musculoskeletal conditions is crucial to minimize a chronic pain syndrome [98]. The pharmacological management of pain in the acute stage is summarised in Table 11.

Given that TBI is one of the most frequent conditions worldwide, and the leading cause for mortality and morbidity in children and young adults, it is surprising that there are so few reports of TBI causing central pain [36].

Post-traumatic headache is defined as a headache commencing within 14 days of regaining consciousness after TBI. Walker et al. [100] observed that most studies on post-traumatic headache were focused on patients with *mild* TBI and identified only two studies focused on moderate to severe TBI [101, 102]. They continued to study 109 young adults with moderate to severe TBI

Table 10 The most frequent causes for pain following TBI

Modality	Aetiology
Musculoskeletal	Fracture, abrasion, laceration, sprain, strain, arthropathy, hematoma, contusion, *pressure ulcer, heterotopic ossification, reflex sympathetic dystrophy, adhesive capsulitis, tendonitis, myofascial dysfunction, tension headache*
Vascular	Thromboembolism, arterial insufficiency, compartment syndrome, migraine
Neurogenic	Radiculopathy, plexopathy, peripheral nerve lesion, complex regional pain syndrome, central pain, high ICP
Visceral	Cardiac, gastrointestinal, pulmonary, hepatic, renal, genitourinary
Iatrogenic	See Table 4

Secondary problems are printed italic. Adapted from [98]

Table 11 Pharmacological treatment of pain in the ICU

Drug	Application	Adverse effects[a]	Route	Dose	Half-life	Evidence
Acetaminophen	Intermittent	Liver failure	p.o.	325–600 mg q 4–6 h	2 h	Class IV
Fentanyl	Continuous	Rigidity with high doses	i.v.	0.7–10 μg/kg/h	1.5–6 h	Class IV
Hydromorphine	Continuous	Respiratory depression	i.v.	7–15 μg/kg/h	2–3 h	Class IV
Ibuprofen	Intermittent	Bleeding, GI, and renal	p.o.	400 mg q 4–6 h	1.8–2.5 h	Class IV
Ketrolac	Intermittent	Bleeding, GI, and renal	i.v.	15–30 mg q 6h	2.4–8.6 h	Class IV
Morphine	Continuous	Histamine release	i.v.	0.07–0.5 mg/kg/h	3–7 h	Class IV
Steroids	Intermittent	Glycemic control	i.v. & p.o.	Depends on drug chosen		Class IV
Remifentanil	Intermittent	Hypotension, rigidity	i.v.	0.6–15 μg/kg/h	3–10 min	Class IV

Modified from Ref. [295]. Note that constipation is a side-effect of all morphine derivatives and regular movicolon administration may be found beneficial on ICU. For a full list of all side-effects please refer to the manufacturer

[a] Only the most common adverse effects are listed. For a full list refer to the producers documentation (avoid > 4 g/day)

(Glasgow Coma Score < 13, coma > 30 min, post-traumatic amnesia > 24 h, residual cognitive deficit or substantial damage on brain imaging). Following TBI, post-traumatic headache was an *acute/subacute* problem in 41/109 (38 %). About 20 % of these patients still suffered from headaches at the 6- and 12-month follow-up and 60 % suffered from post-traumatic headache at some time during follow-up [100]. Importantly, the incidence of post-traumatic headaches depended on the study group and ranged from 9 to 90 % [103–108]. The numerous methodological problems underlying many of these studies have been highlighted [109, 110]. Not all authors are convinced that post-traumatic headache exists as a separate entity [111, 112]. A well-controlled prospective study found that in 91 % of patients the headaches following TBI fulfilled the diagnostic criteria for episodic tension-type (11 %), chronic tension-type (51 %), migraine without aura (2 %), chronic tension-type and migraine without aura (8 %), chronic tension-type and probable migraine (19 %) [113]. Medication overuse, particularly of codeine containing drugs, was found to be the cause of post-traumatic headache in about 42 % of cases [113, 114]. Treatment consists of gradual withdrawal of drugs which may occasionally require adjunctive pharmacological treatment [115].

Root Avulsion

Severe pain develops in about 70 % of patients following brachial plexus avulsion [116]. Root avulsion is a common problem following motor bike accidents. Curative treatment options are still experimental [117]. The pain becomes intractable in about 20 % of these patients [116]. Lesioning of the dorsal root entry zone (DREZ) has successfully been used as an invasive treatment approach and most patients will have moderate to good long-term pain relief [118–123]. Root avulsions at the level of the conus medullaris are rare and lesioning of the DREZ may again be an option in some cases [124].

Spinal Cord Injury (SCI)

Pain is arguably rated by patients as the biggest problem following SCI [125]. All patients suffer from pain in the acute phase, about 90 % at the time of transferral from neurocritical care to rehabilitation [126], about 63–71 % 1-year post-injury [127–129] and about 40 % at the 6-years post-injury follow up [130]. Pain is localized at level of the injury in 34–41 % and below-level in 34–66 % [130, 131]. The resulting neuropathic pain is difficult to treat [132]. There is class IIc evidence that blockage of NMDA receptors with ketamine (6 μg/kg/min after a bolus dose of 60 μg/kg) in the acute phase may reduce the development of central pain [133]. Influencing factors such as diurnal variability should be assessed individually [134]. The best level of evidence was found for treatment with anticonvulsants, analgesic drugs, gabapentin, and pregabalin [135–138]. For further guidance on management of central pain see Table 8. Note that pain is aggravated by muscle spasms, infections, full urinary bladder, and constipation [139]. DREZ lesioning provides an alternative option for those patients with pharmacological intractable pain [140–142].

Syringomyelia

Pain affects about 40 % of patients with syringomyelia and is very disabling [143]. The pathophysiology of this generally neuropathic and occasionally central pain is complex and may imply alteration of high-level pain modulation alongside damage to the spino-thalamic tracts [144]. The recently proposed thermosensory disinhibition theory suggests that reduction of the inhibition of thermal sensory afferents that affect nociceptive systems may play a relevant pathophysiological role.

In the acute stage pain worsens with the Valsalva manoeuvre and straining. Following surgery (i.e., foramen magnum decompression in patients with Arnold–Chiari malformation), pain was reduced in up to 70 % of patients

from a VAS score (scale 0–100) of about 65 to about 30 within 2 years (Fig. 4 in Ref. [145]). There is retrospective evidence that intrathecal application of ropivacaine may be of benefit in some patients [146].

Neuroinflammatory and Neurodegenerative Conditions

The most frequent acute conditions are infections of the brain meninges (meningitis) or brain parenchyma (encephalitis) which are also summarised as meningoencephalitis because of the clinical overlap [147]. Meningitis and encephalitis are discussed first because they are a neurological emergency requiring urgent treatment [148]. Because of the chronic nature of the other neuroinflammatory and neurodegenerative conditions discussed here, some patients may already receive pain treatment and a holistic patient management approach may collide with a more focused strategy, likely requiring discussion in individual cases.

Meningitis

Headaches or neck-stiffness are present in almost all patients with meningitis [149].

Pain management in meningitis combines adjunct measures and analgesic drugs (see "Adjuvant Therapy" section and Table 6). There is some interesting experimental evidence that activation of the trigeminal system in meningitis may, via release of proinflammatory cytokines (neurogenic inflammation), be harmful and an anti-inflammatory effect has been suggested when triptans have been given at an early stage [150]. There is evidence that the use of corticosteroids as an anti-inflammatory agent may be of benefit in meningitis [151]. Others remain sceptical [152]. Neither of the discussed studies specifically addressed the effect of steroids on pain management, but were focused on outcome. There is an effect of steroids on treating other forms of headaches [153] and a possible adjunct use for pain management in meningitis warrants prospective study.

Encephalitis

Most patients suffer from diffuse headache, generalized pain, and agitation.

Herpex simplex virus (HSV) encephalitis is the most frequent viral encephalitis in adults in developed countries [147]. HSV encephalitis presents as an acute, necrotizing, focal encephalitis mainly affecting the frontal and parietal lobes, with inflammation and swelling of the brain [154, 155]. Acyclovir is the treatment of choice [154, 155]. Pain occurs mainly in form of diffuse headaches or occipital/cervical pain associated with neck stiffness and adjunct measures are recommended (see "Adjuvant Therapy" section).

West Nile Virus (WNV) infection presently poses concern to the US health authorities because of its possible transmission via blood transfusion. Headaches, eye pain, lower back pain, pain, muscle pain, and arthralgias occur in about 61 % of WNV patients [156]. They may be the presenting signs [156–159]. The differential diagnosis of encephalitis caused by other *Flaviviridae* consists of Japanese encephalitis, St. Louis encephalitis, Murray valley encephalitides and dengue fever [160, 161]. Other emerging atypical encephalitis are caused by the Venezuelan equine, Nipah and enterovirus 71 [161]. There is no causative treatment and vaccination strategies are still under development.

Pain management is focused on adjunct measures. Because of some similarities of WNV infection with poliomyelitis additional measures may be discussed (see "Poliomyelitis" section).

Human African Trypanosomiasis or "sleeping sickness" is a two-stage disease with an early hemolympathic and a late encephalic stage [162]. Transmission occurs by mosquito bite, mainly in tsetse infested areas. Headaches are the main symptom occurring in 78.7 % of patients [163] followed by sleepiness (74.4 %). Other sensory symptoms include painful hyperesthesias, paresthesia, anesthesia, and pruritus are common in the late stage. In a meta-analysis eflornithine and nifurtimox combined with eflornithine were found to be well tolerated and reduced the relapse rate [164]. Importantly encephalopathy and coma are the most feared complications of treatment with melarsoprol [165]. The main differential diagnosis is cerebral malaria. There is no causative treatment.

Malaria is an infectious disease caused by a vector-transmitted parasite (plasmodium). Headaches, joint and body aches are a common and nonspecific feature of malaria [166–168]. There is geographic variation in the proportion of patients with systemic malaria who also develop cerebral malaria. A reduced level of consciousness, focal neurological signs, and seizures in the absence of hypoglycemia or other infections point to *cerebral malaria* [167]. Headaches are a frequent presenting sign, but it needs to be born in mind that they can also be drug-related [169]. Morbidity for cerebral malaria remains high if admission to ICU is required [170–172]. The treatment of malaria is based on antischistosomal drugs of which chloroquine in favored for plasmodium vivax and artemisinin-based combination therapies for plasmodium falciparum [173–175].

Encephalopathies

Pain has not been a generally recognized feature in patients suffering from encephalopathies; however, many of these patients are very agitated. There is as yet no evidence for knowing whether or not the agitation may in part be related to diffuse headaches, alterations in the pain threshold or to

musculo-skeletal pain as a result of being bed-bound. Severe pain due to bilateral striatal necrosis was reported in one case of an acute encephalopathy [176].

Headaches are a recognized feature in the posterior reversible encephalopathy syndrome. Patients present with acute onset headaches, altered mental state, seizures, visual symptoms, a variety of focal neurological signs, and a diagnostic MRI picture [177–181]. There is one report of post-anoxic encephalopathy causing severe and intractable pain [182].

Toxic encephalopathies The toxic encephalopathies mostly occur in three situations: (1) poisoning in an attempted suicide, (2) poisoning in an attempted murder or (3) environmental poisoning. A fourth category includes terrorism and the illegal use of toxins in war [183, 184]. The most frequent toxins are aluminium, arsenic, cadmium, iron, lead, mercury, and thallium [185–187]. If ingested orally, all cause gastrointestinal symptoms. Neuropathic and musculoskeletal pain are observed with arsenic and thallium. Central pain has been seen in arsenic poisoning, and hyperalgesia with thallium poisoning. Admission to the neurocritical care unit is usually a result of seizures, encephalopathy, severe peripheral neuropathy, and the need for ventilation. For treatment of acute central pain see Table 8.

Multiple Sclerosis (MS)

About 44–88 % of MS patients suffer from chronic pain, including musculoskeletal pain [188, 189], which was rated as severe in up to 38 % in one study [190]. In about 28 % of MS patients this is due to central pain (see Table 7) and to trigeminal neuralgia in about 5 % [36]. Patients with MS may be seen in intensive care because of respiratory problems [191], with acute respiratory failure remaining an anecdotal observation (Ref. [192] and references therein). Many of these patients will already be on analgesic medication and it is recommended to continue these whilst the patient is on ICU. New, potential targets for pain management in MS include the sphingosine-1-phosphate receptor [193], but this will require rigorous testing as outlined by Solaro et al. [189].

Behçet's Syndrome (BS)

BS is a multi-system, vascular-inflammatory disease of unknown origin [194]. About 5 % of patients with BS have neurological signs due to a meningoencephalitic process, or more rarely due to occlusion of cerebral veins and sinuses. Although all of these can cause headaches [195, 196] other mechanisms may be involved, because the prevalence of up to 82.5 % of headaches in patients with BS far exceeds that of neuro-BS [197]. In addition, there is a risk to develop SVT which may worsen headaches (see "Sinus Venous Thrombosis" section).

Admission to ICU is rare and most likely when there are vascular problems [198–201]. The treatment is targeted at attacks and the affected organ system [194–202]. Siva and Saip [194] advice high dose intravenous methylprednisolone (1 g/day for 7 days) in patients with imaging and clinical evidence for acute neuro-BS. There are no consensus guidelines on pain management in BS. Therapeutic LPs may be helpful in patients in whom worsening of headaches was due to development of a SVT (see "Sinus Venous Thrombosis" section).

Tumor

Management of these patients is, with few exceptions, focused on post-surgical pain (Table 6). Patients in whom the tumor has infiltrated the trigeminal, glossopharyngeal or vagus nerves may suffer from a neuralgia. In these selected cases the first line treatment is AEDs such as carbamazepine or lamotrigine. Central pain is a rare complication occurring in only 2–4 % after surgery, radiation or chemotherapy in cancer patients [203]. Occasionally central pain may occur in metastatic disease and has been found to be greater in patients with tumors in the spinal cord as opposed to the brain [203]. For guidance on treatment of central pain see Table 8.

Paraneoplastic Disease

Some patients with a tumor develop a paraneoplastic disease. Pain in paraneoplastic disease is caused by a paraneoplastic sensory neuropathy. The differential diagnosis includes Sjögren's syndrome and, if chemotherapy was used to treat the primary tumor, also cisplatin toxicity [204]. Overall treatment is directed at the underlying oncological disease. The neuropathic pain is mainly treated using antiepileptic drugs or tricyclic antidepressants.

Prion Disease

Pain, itching, and paresthesia were observed in about 11/71 (15 %) of patients with pathologically confirmed prion disease in one retrospective study [205]. Headaches were already present at onset of sporadic Creutzfeldt–Jakob disease (CJD) in 17 % of patients, with 27 % experiencing headaches at some point in the disease course. It would not be surprising if in these cognitively impaired patients the presence of pain would add to the agitation and confusion. There is a suggestion of early onset migraine being associated with the prion protein gene 129VV polymorphism [206]. In patients with evidence for autonomic features, specific treatment is recommended as reviewed for the trigeminal autonomic cephalgias [207].

Neuro-Muscular Conditions

Because of the risk of respiratory failure any patient suffering from a neuro-muscular condition may be seen in ICU. Most frequently this is due to an acute GBS, but also patients with MG and very occasionally a POEMS syndrome (see below) are seen. Poliomyelitis is nowadays rarely seen in developed countries, but a wealth of information for pain management is available which will be reviewed.

Guillain–Barré Syndrome (GBS)

Pain, hypoesthesia, dysesthesias, and allodynia are prominent features in 45–89 % of patients during the acute phase of GBS [208–211]. The pain characteristics include most frequently dysesthetic extremity pain, followed by back and leg pain, myalgic-rheumatic extremity pain, visceral pain, pressure palsies, and dysautonomic headaches. Although the mean pain intensity may be moderate (4.7 ± 3.3 on a VAS of 0–10), much higher scores (7.0 ± 2.0) have been reported in about 47 % of patients [210]. A prospective Dutch study found higher pain severity scores in patients with sensory disturbances, preceding gastroenteritis, females, and those with severe disease [211].

Occasionally pain, dysesthesias, and sensory deficits may precede onset of the other symptoms by a couple of days [211–215]. Chronic pain may develop in a proportion (33–53 %) of GBS patients [208, 211]. In another case report severe neuropathic pain developed following the acute motor and sensory axonal neuropathy variant of GBS [216].

Much of the pain seen in ICU seems to be of muscular and skeletal origin due to reduced mobility in GBS [210]. This pain is very disturbing to the patient and a difficult management problem, requiring intensive nursing care and frequent repositioning of the patient body and limbs. About 75 % of GBS patients required opioids for management of their pain at one stage [210, 214, 217]. None of the presently available drugs seems to provide satisfactory long-term pain relief. There is class IIc evidence that gabapentin (15 mg/kg daily) is effective in the acute phase of GBS [218]. In an earlier trial the same group had shown that carbamazepine (300 mg daily for 3 days) was superior to placebo [219], but ultimately gabapentin proved to be the more effective drug [220]. A recent multidisciplinary consensus paper recommends the use of either drug alongside narcotic analgesics in the acute phase [221]. Steroids have no additional effect [211].

The pathophysiological basis for these *positive* symptoms in GBS which is otherwise determined by *negative* symptoms such as paralysis and sensory loss due to demyelination and axonal loss is poorly understood [210, 212, 222, 223]. It is, therefore, enlightening to learn from recently developed histological techniques using skin biopsies [224–227] that 11/20 (55 %) of GBS patients showed signs of active nerve degeneration in the dermis [209]. Ephaptic transmission across damaged axons or direct damage to the nerve roots may provide alternative explanations for the occurrence of pain [213].

POEMS Syndrome

The combination of Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein (M band), and Skin changes (hypertrichosis, hyperpigmentation, diffuse skin thickening, finger clubbing, dermal hemangiomas, and white nail beds) is recognized as POEMS syndrome [228]. Additional clinical signs include sclerotic bone lesions, lymphadenopathy, papilloedema and edema [229]. Clinically the neuropathy in POEMS may resemble what is seen in chronic inflammatory demyelinating disease [228, 229]. The treatment of POEMS includes immune-modulatory and immunosuppression strategies [230]. There are anecdotal reports of successful autologous hematopoietic stem-cell transplantation [231, 232].

Patients with POEMS syndrome suffer from pain mostly due to the plastocytoma infiltrating the bone. The pain can be treated similar to post-surgical pain (Table 6).

Myasthenia Gravis (MG)

The pain management of patients with MG in neurocritical care is an important issue and mainly focused on the post-operative pain following thymectomy [233]. Pain following sternostomy is more severe compared to video-assisted thoracoscopic thymectomy [234, 235]. The latter poses a particular challenge to the anesthetist, and in one study epidural analgesia with 0.125 % ropivacaine provided better pain relief than 0.125 % bupivacaine [236]. Epidural analgesia is also preferred to oral opioids because of the improved post-operative respiratory function [233]. Following sternostomy about 27 % of patients developed chronic pain [237, 238], which was moderate to severe in 48 % [237]. Less frequently patients are admitted to the neurocritical care unit in a myasthenic crisis, which was the presenting symptom in 28 % of 27 patients observed over 5.5 years [239].

In the ambulatory patients with MG pain is an infrequent symptom. Pain may present as lower limb pain [240] or unilateral headache [241]. Anecdotal pain has also been associated to pyridostigmin bromide [242]. There is one case report where gabapentin was associated with exacerbation of MG [243]. Therefore, gabapentin should be avoided or used with care in patients suffering from MG [243].

Poliomyelitis

The rationale for discussing poliomyelitis here is that the vast experience from the past dealing with the considerable amount of pain in these patients may be of value for the clinical management of new, emerging diseases such as WNV infection.

About 83 % of 291 patients seen at Colorado School of Medicine in 1952 suffered from acute pain and spasms in the first 2–3 weeks following the febrile illness [244]. All of those who had an encephalitis also suffered from severe muscle pain [244]. Contractures were a serious problems at the time, particularly because the iron lung only allowed for a very limited degree of physiotherapy.

Pain probably originates not only from the muscle itself, but also from pathology affecting the spinal cord and dorsal roots, the meninges and the sympathetic system [245]. The presence of sensory involvement with hyperesthesia [245] is suggestive of neuropathic pain. The presence of brainstem damage affecting the reticular formation [245] suggests of central pain.

As expected from the various pathological and anatomical sources of pain in poliomyelitis, there is not one single drug capable of providing complete pain relief. Tolazoline hydrochloride (Priscoline) has been given with some effect on the sympathetic involvement [245–247], as was tetraethylammonium chloride (Etamon) [246]. Salicylates have been effective, as have opiates [246]. There has been some controversy to whether muscle relaxants (which was curare at the time) in combination with passive physiotherapy during the acute phase improves the outcome [246–248]. Quinine and warming were effective in pain directly caused by cramps and muscle twitching in the acute phase [245–249].

Later in life these patients may develop post-polio syndrome and suffer from musculoskeletal and joint pain [250]. Some of the intractable pain suffered by the Mexican painter Frida Khalo (1907–1954) was attributed to the poliomyelitis she acquired at the age of six [251]. One study suggests that lamotrigine may be of some benefit in the post-polio syndrome [252].

Headache Syndromes

It may be counter-intuitive to discuss headaches in a separate paragraph within this review. Our rationale is that headaches are probably the most frequent symptom leading to a neurological consultation. In brief, *primary headache syndromes* must be distinguished from *secondary headache syndromes*. The most frequent *primary headache syndromes* are the trigeminal dysautonomias, thunderclap headache, hypnic headaches, benign exertional or sexual headaches and cough headaches [253]. The etiologies of the most frequent *secondary headache syndromes* requiring further investigation are summarised in Table 9.

Hydrocephalus

The most frequent pain caused by hydrocephalus is a headache due to ICP [254]. Abdominal pain in hydrocephalus is mostly related to a local problem of the ventriculo-peritoneal shunt, requiring revision [255]. There are also anecdotal reports of facial pain [256, 257], trigeminal neuralgia [258] and localized limb pain in the context of hydrocephalus [259]. A rare pitfall is the presence of low-pressure headache (see below), observed after over-drainage via an extraventricular drain (EVD) or following valve dysfunction after insertion of an ventriculo-peritoneal shunt [260]. Further worsening of the headache following increased CSF drainage, probably made with the best of intentions, usually leads to the diagnosis.

Low-Pressure Headache

Low-pressure headache is orthostatic in nature and associated with low CSF pressure. It can occur in any patient with an EVD, following trans-sphenoidal hypophysectomy/foramen magnum decompression or microvascular decompression of the trigeminal nerve. The headache is made worse by sitting up and is associated with nausea/vomiting and sometimes dizziness. Low-pressure headache responds to i.v. fluids, caffeine in the form of Coca-Cola or strong tea/coffee. A regular anti-emetic such as cylizine and bed rest may be necessary initially. Patients who fail to respond to conservative treatment may need an epidural blood patch to seal the leak [261].

Epileptic Syndromes

Pain is a feature of a range of epileptic syndromes and is an ictal phenomenon, as first pointed out by Gowers [262]. Pain is most frequently located to the abdomen (1.4–16 %) [263–266] or head (1 %) [265]. There are some reports localized pain to the hand [263, 267, 268] and pharynx [269]. These painful somatosensory auras are mostly due to temporal, parietal, and frontal lobe seizures [264, 265]. Painful auras are less frequent in parieto-occipital lobe epilepsy, or peri-rolandic epilepsy [265]. Photosensitive occipital epilepsy is a rare disorder first described by Panayiotopoulos [270] in which pain appears to be relatively frequent. In 7/9 (78 %) of patients the seizure was followed by severe pain. There may be a role for HCN channels in mediating pain sensation in epilepsy [271].

The complete differential diagnosis of paroxysmal abdominal pain is broad and beyond the scope of this review. Abdominal pain due to a somatosensory aura in

temporal epilepsy is typically sharp or colicky and resolves with anti-epileptic medication. Porphyria is an important differential diagnosis. Patients with porphyria may become agitated or disorientated following a prolonged "nil by mouth" status on the ICU. Also the worsening of seizures in porphyria while taking standard antiepileptic drugs [272] should lead to the correct diagnosis. The epigastric pain in porphyria is severe, frequently requiring multiple analgesics including narcotics [272]. In a recent review of the English literature, Zinkin and Peppercorn [273] identified 36 cases of *abdominal epilepsy* identified over the last 34 years, in which pain was the most common symptom. We have found seven new cases in the English literature, two of whom were children [274, 275], and interestingly five were from a large Brazilian family in whom the temporal lobe epilepsy was linked to chromosome 4p15 (patients vii:34, v:3, vi:58, vi:83, vi:86 in Ref. [276]).

Iatrogenic

As mentioned in the "Introduction" section, iatrogenic pain is the most frequent pain experienced in ICU [13, 14] for which guidelines have been introduced. Specific points for the management of the post-operative neurosurgical patient are reviewed, followed by discussion of a rare complication to medication, the neuromalignant syndrome.

Post-operative Neurosurgical Patient

Post-operative pain (Table 5) can be anticipated and its management can, therefore, be carefully planned [277]. Patients need to be reassessed regularly during the post-operative period using established pain scores, to achieve adequate pain control using standardized protocols (Table 6).

For post-operative wound infiltration one can use bupivacaine 0.25 % with adrenaline 1 in 200,000. This significantly reduced post-operative pain [278]. Infiltration of the abdominal wound is particularly effective following insertion of ventricular peritoneal shunts.

There has been some debate to whether morphine is safe to be used after intracranial surgery. There is class III evidence that the careful use of morphine is safe and superior to codeine [279]. We prefer the intravenous route because of the more complex pharmacokinetics of the subcutaneous route in ICU [280, 281]. Another option is to use intramuscular morphine as follows: >60 kg $\rightarrow$ 10 mg; 45–60 kg $\rightarrow$ 7.5 mg; and <45 kg $\rightarrow$ 5.0 mg. These doses should be tailored to the patient's neurological status [282]. In order to minimize the risk of errors we recommend a standardized protocol for PCA [277]. There is evidence that single-dose Gabapentin (250 mg) may also be of benefit for acute post-operative pain [283].

Once the patient is transferred to medium care the subcutaneous route becomes more attractive because it is easy to maintain, comfortable for patients, can be sited by nursing staff and appears to improve post-operative sleep [284]. PCA should *not* be used in patients with hypothermia or low cardiac output states. It is advised to have in-house guidelines for use of PCA.

Some post-surgery patients suffer from *neuropathic pain*. *Neuropathic pain* is commonly described as burning, stabbing, stinging, shooting, aching or electric shock-like in quality. It may be felt superficially or in deep tissues, may be present intermittently or constantly and can occur spontaneously or be triggered by various stimuli. Neuropathic pain may already have been present pre-operatively and is sometimes temporarily worse following surgery. Therefore, any pre-operative treatment should be continued in the immediate post-operative period.

Acute neuropathic pain is sometimes seen for the first time post-operatively and is usually temporary. It presumably results from inflammation around nerve roots following surgery. *Severe, persistent neuropathic pain* post-operatively needs to be investigated to exclude compression of nerve roots by a hematoma or infections. Treatment options for neuropathic pain in the post-surgical patient comprise: dexamethasone 4 mg q.d.s. oral/iv for two days if inflammation around a nerve root is thought to be the cause. For continuous neuropathic pain a good choice is amitriptyline at a starting dose of 25 mg (10 mg in elderly). If tolerated the dose can be increased every 2 days, up to a maximum dose of 150 mg. For paroxysmal neuropathic pain carbamazepine may be a better choice (starting dose 200 mg orally, increasing slowly to maximum dose of 2.4 g daily). If the neuropathic pain remains unresponsive than gabapentin is an alternative [283]. Some patients who do not tolerate gabapentin may respond to pregabalin.

Neuroleptic Malignant Syndrome (NMS)

Musculoskeletal pain and subsequent agitation due to muscle rigidity would be an expected symptom in the NMS. However, none of the 115 case reports reviewed by Addonizio et al. [285] mentioned pain explicitly and we did not find any evidence for it in the newer literature, other than in cases presenting with an acute, painful abdomen [283, 286]. NMS is an important, but easily missed differential diagnosis [287]. A particularly difficult problem is the manifestation of NMS in the context of TBI [288]. In TBI patients one frequently observes high fever (>39 °C), thought to be of central origin, which may last for days. Some of these TBI patients will also have received a neuroleptic drug such as risperidone for management of their agitation.

The list of drugs causing NMS is long and includes bromperidol, chlorpromazine, clomipramine, clozapine, fluphenazine decanoate, levopromethiazine, loxapine, meclopramide, olanzapine, perphenazine, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, ziprasidone, *cis*-clopentixol, clotiapine, fluphenazine HCl, haloperidol, and promazine [285, 289–291]. The condition is so rare that there is only class IV evidence that treatment with dantrolene may be helpful [285]. Alternative drugs that have been tried are bromocriptine, L-DOPA, amantadine, benzodiazepines, propanolol, and curare [285].

Common Secondary Problems

Table 10 lists some secondary musculoskeletal problems. Prevention of these problems requires a multidisciplinary approach combining skilled nursing, targeted physiotherapy, and swift pharmacological therapy alongside specialized treatments such as intramuscular botulinum-toxin for spasms and contractures. The relevance of weakness and spasticity for the development of these complications is probably underestimated. Additionally fibrosis, and ossifications contribute to the adaptation of compensatory postures, and there is a risk that this may lead to a vicious cycle of further decrease of motility and increase of pain. Heterotopic ossifications are difficult to prevent, but salicylates, intrathecal baclofen and botulinum toxin have all been used and surgical intervention is rarely necessary [292].

Pain Management

Over the last decade guidelines for the management of acute pain and pain in the critically ill patient have been developed [293–297]. The earliest of these guidelines were largely based on expert opinion (i.e., class IV evidence) [293]. To the best of our knowledge no such guidelines exist for neurocritical care, and recommendations made by scientific task forces will be needed in the long term.

In neurocritical care adjunct measures should be combined with pharmacological treatment.

Adjuvant Therapy

There are a number of practical adjuvant measures:

- Good and intensive nursing care is key to patient management.
- Neck roll to support the back of the neck, and arm supports to reduce the weight of the arms following complex cervical spine surgery.
- Warm pack, cold pack, airline eye covers (for severe headache and photophobia, diplopia), physiotherapy, and moral support.
- Loosening of tight head bandages
- Insertion of a nasogastric tube during induction of anesthesia to aid administration of oral analgesics post-operatively if swallowing difficulties are anticipated
- Massage is often effective in the relief of troublesome muscle spasm.
- A small dose of benzodiazepine prescribed regularly can be very effective in reducing muscle spasm.

Pharmacological Therapy

There are numerous drugs used for analgesia and sedation in ICU (for a recent review see Ref. [298] and references therein). Of particular relevance in the neurocritical care setting are opioids, benzodiazepines, propofol, haloperidol, NSAIDs, paracetamol, anti-epileptic drugs, tricyclic antidepressants, cannabinoids, local anesthetics, adrenergic and codeine-containing drugs. Administration of analgesics on a continuous or scheduled intermittent basis is recommended, with supplemental bolus doses as required [295, 299], the minimum effective dose for giving the minimum time [16]. All drugs used have a spectrum of side-effects and a broad range of half-lives and drug interactions, all of which are influenced by the organ failure and impaired metabolism frequently observed in neurocritical care.

Opioids

The most frequently used compounds are morphine, hydromorphone, and fentanyl [295]. The pharmacodynamic properties are summarised in Table 11. A systematic Cochrane review did not reveal any relevant difference between hydromorphone and morphine compounds for the treatment of acute pain [300]. Fentanyl or hydromorphone are the preferred opioids in hemodynamic unstable patients or those with kidney failure [295]. Based on the rapid onset of analgesia with fentanyl, scheduled administration is preferred in the acutely distressed patient [295].

Remifentanil has not yet been studied sufficiently widely and prospectively, but because of its very short half-life it may become an important drug for the management of the neurocritical care patient. Particularly for those selected cases, where an immediate intermittent clinical evaluation is required and one wants to avoid the pharmacological effects of morphine. Scheduled interruption of the continuous administration of remifentanil should allow regular neurological assessment [301]. For intermittent therapy, morphine and hydromorphone are better suited because of their longer half-life (Table 11).

Benzodiazepines

Benzodiazepines provide no pain relief. They are used for sedation and relief of anxiety. The associated *anterograde* amnesia is frequently desirable but one needs to remember that there may also be a variable degree of *retrograde* amnesia. They also have an opioid-sparing effect, probably by moderating the anticipatory pain response [302, 303]. The pharmacokinetics of the different benzodiazepines vary considerably (see Table 12). In many critically ill patients suffering from impaired renal and hepatic function drug kinetics may change considerably, facilitating rapid drug accumulation [304–311]. Additionally, the midazolam metabolism can be inhibited by a range of cytochrome P450 isoenzyme 3A4 inhibitors such as propofol, fentanyl, macrolide antibiotics, and diltiazem [312–315]. Therefore, midazolam and diazepam are mainly recommended in the acutely agitated patients. Patients requiring longer infusions may be better managed with intermittent boluses of lorazepam because it's metabolism is less dependent on renal and hepatic clearance [298]. Benzodiazepines and opioids are synergistic, thus reducing the required dose.

Propofol

Propofol provides no pain relief and is only used for sedation (see Ref. [316] and references therein). In contrast to benzodiazepines which act synergistic with opioids, higher total opioid doses are needed if sedation is maintained with propofol alone [317].

Propofol is the favored drug for sedation in patients with head trauma because of an ICP lowering effect and rapid rate of recovery [316]. The rapid kinetics of this intravenously administered oil-in-water emulsion allow for easy titration of the required dose. Most neurocritical care units use 1 % propofol in a 50 mL syringe to be titrated at a rate of 0–600 mg/h (the exact starting dose is 5 μg/kg/min, which can then be titrated to 50–100 μg/kg/min). However, there is little evidence for this arbitrary upper limit, particularly in the patient under long-term sedation.

The important side-effects of propofol include hemodynamic suppression with decreased mean arterial blood pressure, negative inotropic and chronotropic effects [316]. Prolonged infusion of propofol has a cumulative cardiotoxic effect with increased mortality [318]. Propofol may increase systemic triglyceride levels, which should be monitored [316].

Haloperidol

This is rarely used as a sedative nowadays. Haloperidol has no analgesic and no amnestic properties. It may be of help in the acutely agitated patients because it can be administered intramuscularly [295]. Due to its high affinity for central D2 receptors, prolonged extrapyramidal symptoms are an important side-effect [319]. Typically these are bilateral and symmetric in contrast to the more asymmetric presentation by Parkinsonism which may have been pre-existing. More severe complications such as sustained dystonia or ophistotonus are only seen rarely. Hypotension and prolongation of the QT-interval are of additional concern (cave poly-pharmacology on ICU) [295, 320]. In the mildly agitated patient a dose of 1–3 mg may suffice, increasing to over 10 mg in the severely agitated patient (see Table 11). There is no clearly defined upper reference limit. A rare but life-threatening side-effect is the NMS (see above) [291].

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

All NSIADs inhibit cyclo-oxygenase (COX). NSAIDs have potentially severe adverse effects such as gastrointestinal bleeding, bleeding secondary to platelet inhibition, development of renal insufficiency, allergic reactions and cardiac and cerebral vascular events. Despite efforts to

Table 12 Sedative drugs used for the pharmacological treatment of agitation and delirium in the ICU

Class	Onset (min)	Adverse effects	Route	Dose	Half-life (h)
Diazepam	2–5	Accumulation, phlebitis	i.v.	0.03–0.1 mg/kg q 0.5–6 h	20–120
Midazolam	2–5	Accumulation	i.v.	0.01–0.1 mg/kg/h	3–1
Lorazepam	5–20	Accumulation, solvent-related acidosis, renal failure	i.v.	0.04–0.2 mg/kg/h	8–15
Propofol	1–2	Hemodynamic, elevated triglycerides	i.v.	5–80 μg/kg/h	2–32
Haloperidol	3–20	Extrapyramidal, NMS	oral, i.v., i.m.	1–3 mg i.v. (mild agitation) 5–7 mg (moderate agitation) ≥10 mg (severe agitation)	12–35

Benzodiazepines have an opioid-sparing effect and provide anxiolysis

circumvent these problems by developing specific COX-2 inhibitors, recent experience shows that this issue is far from being solved [321–323]. There is class I evidence that oral indomethacin or naproxen are effective in treating post-operative pain in adults [324, 325]. Most NSAIDs can only be administered orally, and a liquid formulation exists for ibuprofen and naproxen. Ketrolac and diclofenac can be administered i.v. and were found to be safe in a post-operative setting [326]. In some countries ketrolac is forbidden due to its association with bleeding, but no such complications were seen in the Mayo Clinic double-blind controlled trial on continuous infusion of ketrolac following for adjuvant pain control after renal surgery [327]

Tricyclic Antidepressants

For central pain it has been shown that amitriptyline at a dose of 25 or 50 mg OD may be of benefit in some patients [44, 328]. A systematic Cochrane review provides class II evidence that amitriptyline, desipramine, and imipramine are effective in the treatment of neuropathic pain in a range of conditions (i.e., post-herpetic neuralgia and diabetic and HIV neuropathies) [329].

Antiepileptic Drugs

There is evidence that lamotrigine (200 mg/day) reduces CPSP [330]. Carbamazepine has been successfully used in MS patients suffering from painful tonic seizures and tic douloureux [331], but not in acute pain [332]. Gabapentin is recommended for the treatment of neuropathic pain in chronic conditions (based on 14 studies) [333]. There is no conclusive evidence to whether or not antiepileptic drugs are effective in CPSP [48]. There is no evidence that gabapentin is of benefit in acute pain (based on one study on 70 women undergoing mastectomy) [333]. Single-dose gabapentin (250 mg) are reported to be of benefit for acute post-operative pain [283].

Cannabinoids

The oral cannabinoid dronabinol provided effective pain relief in MS patients with central pain [334]. Importantly, there is experimental evidence that cannabinoids reduce spasticity and are, therefore, likely to have an indirect effect on pain modulation [335, 336]. The potential clinical potential of compounds binding to the cannabinoid receptors CB1 and CB2 is enormous, but progress is hampered by socio-cultural factors [337]. One open-label study suggested that the use of Δ9-tetrahydrocannabinol/cannabidiol oromucosal spray is effective and safe as an adjuvant therapy [338].

Local Anesthetics, Anti-arrhythmic Drugs

Lidocaine (i.v.) and mexiletine (oral) provided some short-term pain relief in CPSP, but the role of these drugs is still uncertain [36].

Adrenergic Drugs

Scadding first postulated that adrenergic drugs may contribute to pain relief [339]. There is class III evidence from an open trial ($n = 15$) that the α_2-agonist Clonidine may provide longer lasting pain relief compared to morphine in patients with MS or SCI [340]. Clonidine is also used in the neurocritical care setting to manage patients who suffer from centrally driven episodes of "sympathic storming" and agitation. Alternatively dexmedetomidine has been found to be effective for the treatment of pain and agitation [341–345]. This drug is, however, only available to some countries.

Codeine-Containing Painkillers

These are frequently favored by the nursing staff and junior doctors on-call, because they may help to reduce agitation as well as pain without causing respiratory depression. However, codeine-containing drugs are known to be a major cause of drug-induced headache [279]. Furthermore, they contribute to constipation. In patients suffering from central pain constipation can be an aggravating factor [47]. A systematic Cochrane review demonstrated that dihydrocodeine was inferior to ibuprofen for post-operative pain if given as a single dose [346].

Conclusions

Here we reviewed the pain characteristics of those diseases most commonly encountered in neurocritical care. Pharmacological pain management in the acute phase is a double-edged sword because of clouding of consciousness. Whether scheduled administration of new ultra-short acting analgesics may solve this dilemma remains to be seen. The clinical assessment is aided by physiological parameters. The additional use of behavioral scales may facilitate documentation and communication. The most common causes of iatrogenic pain have been presented and advice has been given for targeted prophylaxis and treatment of this type of pain. The relevance of *central pain* and *neuropathic pain* has been discussed. Recommendations have been made for the management of central pain in the acute phase.

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