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SPECIAL ARTICLE
THE ITALIAN CONSENSUS CONFERENCE ON PAIN IN NEUROREHABILITATION - PART II

Assessing and treating pain in movement disorders, amyotrophic lateral sclerosis, severe acquired brain injury, disorders of consciousness, dementia, oncology and neuroinfectivology

Evidence and recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation

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on behalf of the Italian Consensus Conference on Pain in Neurorehabilitation (ICCPN)

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ABSTRACT

Pain is an important non-motor symptom in several neurological diseases, such as Parkinson's disease, cervical dystonia, amyotrophic lateral sclerosis, severe acquired brain injury, disorders of consciousness and dementia, as well as in oncology and neuroinfectivology. To overcome the lack of evidence-based data on pain management in these diseases, the Italian Consensus Conference on Pain in Neurorehabilitation (ICCPN) has defined criteria for good clinical practice among Italian neurorehabilitation professionals. Here a review of the literature (PubMed, EMBASE and gray literature) on pain characteristics, treatment and impact of pain in a neurorehabilitation setting is provided. Despite the heterogeneity of data, a consensus was reached on pain management for patients with these diseases: it is an approach originating from an analysis of the available data on pain characteristics in each disease, the evolution of pain in relation to the natural course of the disease and the impact of pain on the overall process of rehabilitation. There was unanimous consensus regarding the utility of a multidisciplinary approach to pain therapy, combining the benefits of pharmacological therapy with the techniques of physiotherapy and neurorehabilitation for all the conditions considered. While some treatments could be different depending on pathology, a progressive approach to the pharmacological treatment of pain is advisable, starting with non-opioid analgesics (paracetamol) and nonsteroidal anti-inflammatory drugs as a first-line treatment, and opioid analgesics as a

second-line treatment. In cases of pain secondary to spasticity, botulinum neurotoxin, and, in some cases, intrathecal baclofen infusion should be considered. Randomized controlled trials and prospective multicenter studies aimed at documenting the efficacy of pain treatment and their risk-benefit profile are recommended for these conditions.

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Pain is a common symptom that may exacerbate the course of many neurological diseases and the perception of the quality of life (QoL). The Italian Consensus Conference on Pain in Neurorehabilitation (ICCPN) was meant to answer a number of questions on the assessment and treatment of pain in the neuro-rehabilitation setting. As part of the ICCPN, we addressed the issue of current evidence and criteria for good clinical practice with regard to pain type, assessment, impact and treatment in movement disorders (Parkinsons' disease [PD] and cervical dystonia), amyotrophic lateral sclerosis (ALS), severe acquired brain injury (sABI), disorders of consciousness (DoC), dementia, and in oncological and neurological infectious diseases. In this regard, the authors' attention has been paid on HIV-related infections, because of their epidemiological importance and more prolonged life expectancy of the affected patients. Aware of their heterogeneity, the organizing committee of the ICCPN decided to combine these pathologies in a single paper because some of them are neurodegenerative disorders, and all are characterized by an absence of focal brain injury and are associated with severe residual disability, as well as the need for protracted care by a multidisciplinary rehabilitation team.

Materials and methods

The full methodology of the ICCPN was described in details elsewhere.[1] The strength of recommendations was scored according to a scale ranging from A to good practice point (GPP) and is reported in parentheses after each recommendation.[1] We systematically searched PubMed and EMBASE using the keywords pain, nociceptive pain, neuropathic pain (NP), central pain, complex regional pain syndrome (CRPS), algodystrophy, rehabilitation, neurorehabilitation, spasticity, Parkinson's disease, cervical dystonia, amyotrophic lateral sclerosis, severe acquired brain injury, DoC, dementia, (neuro-)oncology and neuroinfectivology, rating scales, numerical rating scale (NRS), visual analogue scale (VAS), questionnaire, QoL, antidepressants, anticonvulsants, cannabinoids, opioids, botulinum neurotoxin (BoNT), functional outcome, their corresponding MeSH terms, when available, and all the possible combinations of these keywords for original research studies published from 1983 to 2013. Later on, the search was updated to 2015. Because of the few good quality clinical studies found, we chose a mixed approach, namely a review of published studies identified through PubMed and EMBASE, grey literature and a consensus conference to obtain recommendations from clinical evidence and expert opinions.

Results and recommendations

Question 5.1. What are the main types of pain in movement disorders, amyotrophic lateral sclerosis, severe acquired brain injury, disorders of consciousness, dementia, oncology and neuroinfectivology and how do they evolve? Are there predictors or risk factors for the development of pain in these conditions?

Parkinson's disease

Pain affects up to 80% of patients with PD,[2] with generally much higher estimates than in healthy age- and sex-matched subjects. Pain has also been noted in a substantial proportion of patients with other degenerative parkinsonisms, such as multiple system atrophy,[3] as well as in several hyperkinetic movement disorders, including Huntington's disease, restless leg syndrome and dystonia.[4] Pain is chronic with variable features

and body sites involved.[5] Ford's criteria identified several types of pain in PD, namely musculoskeletal, neuropathic, dystonic, akathisic and central ones.[6] Some Authors also distinguish between pain associated or not associated with PD, using, in this case, the criteria proposed by Negre-Pages that are based on the topography, duration and frequency of pain, aggravating factors, topographical and temporal relationship with onset of PD, influence of motor complications and therapy.[7] Some studies report the presence of so-called unusual pain, which involves body parts such as the face, head, pharynx, epigastrium, abdomen, pelvis, rectum and genitals.[8]

Several risk factors seem to contribute to pain development in PD. These include motor complications or concomitant medical conditions, such as diabetes mellitus, osteoporosis, rheumatic diseases, degenerative joint diseases and arthritis.[9] Recent evidence also suggests the possible contribution of genetic factors. Data on a possible role of PD severity, psychiatric disorders and gender in the genesis of pain are instead not confirmed.[10]

Cervical dystonia

There are no criteria for pain classification in dystonic patients, and the most commonly reported pain types in dystonia are musculoskeletal and/or myofascial ones. Some authors characterize pain as exhausting, radiating, prickly or "pulling the neck". Indeed, the pain associated with cervical dystonia is local in 68% of patients, radiating in 31%, while in 59% of cases it is described as a feeling of "pulling" in the neck.[11] However, compelling evidence suggests that pain in cervical dystonia is not simply muscular in nature. Some Authors postulate that changes in the processing of the discriminative aspects of pain in the central nervous system may underlie the development of painful symptoms in this condition.[12] In keeping with this hypothesis, in patients with painful cervical dystonia, the severity of motor symptoms is not related to the duration or intensity of pain.[13] Prolonged muscular contraction and changes in nociceptive pathways [12] or cortical somatosensory systems [14] may contribute to the development of pain in cervical dystonia. Other factors like local injury, depression or insomnia [15] may also be implicated.

Amyotrophic lateral sclerosis

Pain has always been considered as a rare complication in motor neuron disease (MND), especially in the early stages. This classical concept has been disproved by recent guidelines [16] that recognize its presence and potential treatability. Other Authors have identified physical pain as the main cause of suffering and resignation,[17] affecting more than 80% of patients in some case series.[16, 18, 19] The main mechanisms of pain in MND are muscle spasms, contractures, cramps, spasticity, abnormal stress on the musculoskeletal system caused by hyposthenia, joint locking and pain secondary to immobility. In rare cases, CRPS [20] and reflex sympathetic dystrophy have also been described. Although the intensity of symptoms correlates with functional state and tends to increase with the duration of the disease,[21] pain is also present in the early stages. In several studies that have investigated the presence of pain in MND, about 50% of patients reported pain, with no statistically significant differences depending on stage of the disease.[22] The main types of pain encountered in clinical practice and described in the medical literature [17, 22] are (in decreasing order of frequency): muscle cramps, postural pain in the pelvic girdle, postural pain in the shoulders and neck, postural pain in the legs, pain caused by falls/trauma, gastrostomy site pain, headache, pressure, ulcers and arthritis. The body locations are (in decreasing order of frequency): thigh, calf, knee, leg, foot, heel (26% of patients); arm, hand, wrist (25%); neck (12%); back (9%).[22] Musculoskeletal pain can be attributed to osteoarticular diseases. In advanced stages, joint and bone pain are secondary to muscle atrophy and the consequent loss of protective muscle layers. Pain can be aggravated by wrong posture, such as cervical pain that is very common in head ptosis due to neck extensor weakness. Patients with gastrostomy may complain of pain from positioning of the device or colic pain caused by poor adaptation to enteral nutrition. Patients with tracheostomy can experience pain due to maintenance of fixed postures for long periods of time, accumulation of saliva or mucus, traction or weight of the ventilation tube and frequent aspirations. The pain in ALS patients has been significantly correlated with depression rating scales,[23] and measures of QoL.[24] In the terminal stages of the disease, it has been identified as a major determinant of the desire for assisted suicide.

Severe acquired brain injury, disorders of consciousness and dementia

The literature includes much research into modifications of brain activity following nociceptive stimulation in subjects with DoC, the aim being to understand their possible perception and suffering in painful conditions.[25] Laureys studied subjects in vegetative state (VS) using PET and demonstrated that somatosensory nociceptive stimuli activate the mesencephalon, the contralateral thalamus and the primary somatosensory cortex, but not the secondary somatosensory, bilateral insular, posterior parietal and anterior cingulate cortices.[26] At variance, Kassubek, using a similar methodology, demonstrated the activation of areas involved in affective and cognitive conscious pain perception, including somatosensory cortical areas, either primary or secondary, and anterior cingulate cortex.[27] Boly studied the response to painful stimulation in patients in minimally conscious state (MCS) compared with healthy controls, and showed that the brain areas activated by pain are similar in the two groups.[28] These studies suggest that the pain processing network may be activated to a similar extent in MCS and normal controls, while it is only partially activated in VS, with a disconnection between primary and higher-order associative cortices.[26-28] However, the problems related to the functional neuroimaging methods, the small patients populations, and the different etiologies of DoC across the studies suggest to consider these data as too preliminary to be used in routine clinical practice.[29] In the acute phase and during early post-acute intensive rehabilitation of sABI, pain may be caused by fractures in cases of multiple injuries, abdominal or chest injuries, skin lesions, surgical wounds, invasive devices and care-related manoeuvers (tracheal aspiration, central venous catheter, bladder catheter replacement, nasogastric tube, PEG, venous and arterial blood sampling). In late post-acute and chronic phases, painful symptoms can have many causes, such as diffuse spasticity, joint limitations, bedsores, ischemic skin lesions, peripheral nerve lesions, paraosteoarthropathy, urinary infections, constipation [30] and post-traumatic headache.[31] NP can also be due to nutritional deficit and critical illness polyneuropathy.[32] Moreover, due to the extent of brain damage in these patients, central pain [33] with secondary thalamic syndrome, involving changes in pain processing accompanied by central sensitization and hyperalgesia/allodynia, cannot be excluded.[34]

Pain perception processes may be altered in patients with dementia. Imaging studies of experimental pain in patients with Alzheimer's disease showed that activation of the sensory and emotional system is not diminished, despite widespread anatomical and functional cortical changes. In the initial stages of dementia, greater and more protracted activity of regions concerned with emotional and cognitive processing of pain than in cognitively intact patients is encountered, and the thalamus and especially the sensory/discriminative regions of the cortex appear to be relatively spared. In patients with severe dementia, clinical and imaging data suggest preservation of the sensory-discriminative components and an increase in the pain tolerance threshold in proportion to the severity of cognitive impairment.[35] Involvement of limbic areas and the hippocampus, as well as periaqueductal grey matter and prefrontal cortex may explain flattening of the emotional components associated with pain [36] and a decrease in autonomic responses. Impaired memory and cognitive changes contribute to transforming the emotional reaction to pain into genuine behavioral disturbances (agitation, insomnia, aggressive and oppositional behavior). The main types of pain in patients with dementia reflect those of the geriatric population and differ in advanced stages of disease, due to the prevalence of pain related to bedridden status (spasticity, bedsores) and hospital care.[37-39]

Oncology

Chemotherapy-induced peripheral neuropathies are painful conditions frequently observed in oncology, and their frequency and severity vary according to chemotherapy regimen.[40] Postoperative painful syndromes, caused by lesions of peripheral nerve structures by tumor, as well as headache, specifically with brain tumors, should be regarded as requiring evaluation and treatment.[41, 42] After revision of the literature, we found six classification systems of pain in oncology, most of them aimed at predicting response to analgesic treatments. Among them, the Edmonton classification system for cancer pain considers five pain features and their combinations to define levels of complexity in the management of cancer pain: mechanism of pain (nociceptive/neuropathic), breakthrough pain (absent/present), psychological distress (absent/present), ad-

dictive behavior (absent/present) and cognitive function (intact/partially degraded/totally compromised).[43] Pain intensity and time taken to achieve stable pain control were also considered.[44] Despite little evidence on this topic, studies agree that a classification system might be useful as a clinical guide for oncological pain and early identification of patients for palliative care or pain management.

Neurological infectious diseases

Peripheral and central sensitization are responsible for NP and its chronicization in HIV-infected patients. HIV and related toxins cause nerve damage by overexpression of pro-inflammatory cytokines, chemokines, substance P and reactive oxygen species. This inflammatory response determines nociceptor hyper-excitability and aberrant spontaneous activity in the area surrounding nerve damage, leading to peripheral sensitization. Neurons in the dorsal root ganglia generate high frequency spontaneous discharges after peripheral nerve damage and may contribute to central sensitization. HIV products, such as gp120 protein, may be responsible for a reduction in GABA-ergic transmission and consequent loss of GABA-dependent inhibitory transmission at spinal and supraspinal level. In iatrogenic neuropathies, antiretroviral drugs inhibit DNA mitochondrial polymerase gamma, leading to a deficit in the respiratory process and oxidative phosphorylation.[45] Predictive factors for pain in HIV are age, late stages of HIV infection, low CD4-cell count, higher viral load, comorbidity (*e.g.*, diabetes mellitus, hypertriglyceridemia, alcoholism, malabsorption) and toxic effect of therapy.

Recommendation 5.1.1. Ford's criteria are widely used to classify pain in Parkinson's disease (B), but predictors and risk factors for the development of pain in Parkinson's disease patients need to be defined (C).

Recommendation 5.1.2. Classification criteria, and predictors and risk factors for the development of pain in cervical dystonia should be explored (D).

Recommendation 5.1.3. The main mechanisms of pain in amyotrophic lateral sclerosis are muscle spasms, contractures, cramps, spasticity, abnormal stress on the musculoskeletal system, joint locking and pain secondary to immobilization (D).

Recommendation 5.1.4. Preliminary studies suggest activation of the pain matrix to experimental pain in minimally conscious state, and to a lesser extent in vegetative state, but pain processing in patients with disorders of consciousness should be better explored before suggesting the use of functional neuroimaging in the clinical setting (C). Because of the many possible causes of pain in patients with disorders of consciousness and dementia, their identification requires adequate assessment tools, standardized planning of care, strong team agreement and caregiver involvement (GPP).

Recommendation 5.1.5. High pain intensity at baseline, breakthrough and/or neuropathic pain, young age, psychological distress, cognitive disorders and substance abuse are potential predictors of a difficult-to-treat pain in oncology, and their early detection is recommended (D). Complete neurological evaluation is recommended to differentiate pain due to cancer progression or recurrence from that due to surgery, radiation or chemotherapy, and to assess neuropathic pain (GPP). The assessment of neuropathic pain, its evolution, the effect of treatment and patient's perception, should be based on a multi-dimensional approach combining clinical scales and quality of life measures (GPP).

Question 5.2. Are there methods or standardized criteria for the assessment of pain in movement disorders, amyotrophic lateral sclerosis, severe acquired brain injury, disorders of consciousness, dementia, oncology and neuroinfectivology?

Parkinson's disease

The intensity of pain has been assessed by different methods, such as the McGill Pain Questionnaire (MPQ), NRS, VAS and sensory tests for the evaluation of thermal, electrical or mechanical pain threshold.[7] The King's PD Pain Scale has been recently introduced and validated in an international, cross-sectional, open, multicenter study that suggested it represents a reliable and valid scale for grade rating of various types of pain in PD.[46] The relative validity of the different tools for pain assessment is not known because there have been no studies comparing available methods in the same patient population. Instrumental measures such as laser evoked potentials have been used to experimentally ex-

plore pain processing in PD patients, but they appear preliminary for clinical assessment.[47]

Cervical dystonia.—Different rating scales have been proposed over the years for evaluating qualitative and quantitative characteristics of pain in cervical dystonia. At present, however, there is no standardized method for assessing pain across different dystonic features and varieties. The Toronto Western spasmodic torticollis rating scale is the only scale measuring the overall severity of cervical dystonia that contains a section for pain assessment,[48] and has been used in several studies on BoNT treatment.[49, 50]

Amyotrophic lateral sclerosis

There are no specific criteria for the assessment of pain in MND patients. Among existing general questionnaires, the Brief Pain Inventory (BPI) was used by Chiò [51] to study the prevalence and characteristics of pain in ALS patients. BPI is a structured interview that provides basic information on the quality and quantity of pain in the previous week, indicating its maximum, minimum and average perceived intensities, as well as pain characteristics at the time of the interview. The scale ranges from 0 (no pain) to 10 (worst pain imaginable). The pain is also described in terms of its impact on the normal aspects of daily living (mood, walking, working, relationships, sleep and leisure activities). The use of other rating scales, such as the Italian Pain Assessment Scale [52] or the Neuropathic Pain Scale [22] can be very useful because they explore pain qualities. Another way to assess the intensity of pain is caregiver evaluation, which has proved to agree with patient's experience.[53]

Severe acquired brain injury, disorders of consciousness and dementia

Pain is a subjective experience, and persons with sABI, severe cognitive impairment and language deficit are unable to communicate their sensations and experience of pain. In line with the International Association for the study of pain (IASP), verbal incapacity to communicate does not preclude the possibility to have pain, and in such case appropriate pain assessment and treatment is required.[54] Because evaluation based on indirect and hence interpretative data carry a risk of under- or over-estimating pain and it is unethical to give painful stimuli to subjects who cannot give their consent, current bedside instruments for assessing pain in subjects unable to verbally communicate are based on behavioral signs, such as localization of pain, uneasiness or agitation, particular body movements, facial expressions and emotional reactions, such as grimaces, weeping and lamenting. For patients with sABI and MCS, pain assessment in advanced dementia (PAINAD),[55] nociception coma scale (NCS) [56, 57] and the NCS revised version (NCS-R) [58] are widely used. Pain scores demanding attention and treatment are >4 for PAINAD and >4 or >3 for NCS-R in patients with MCS and VS, respectively.

In patients with dementia, the choice of pain assessment tools largely depends on the degree of cognitive deterioration. In patients with mild dementia, the usual rating scales may be used.[59] In patients with more severe dementia, the validated instruments for measuring proxies for pain are largely the same used for sABI and MCS, and they may differ for their applicability and sensitivity-specificity profile.[60]

Oncology

Although no specific assessment scales for oncological and neuro-oncological pain are available, the VAS, the NRS, and the verbal rating scale (VRS) are the most common one-dimensional scores for pain intensity.[61] The MPQ [62] and BPI [63] are the most widely used multidimensional pain scales in oncology. For assessing chronic pain, it is also necessary to detect any episode of intense pain, the so-called breakthrough cancer pain, but standardized tools for scoring its intensity are lacking. With regard to the frequency of assessment, daily evaluations of the previous twenty-four hours seem to be valid and effective and should be preferred to longer time intervals (*e.g.*, weekly, monthly).[64]

Neurological infectious diseases

We failed to find any diagnostic gold standard for pain assessment in HIV-related peripheral neuropathies. The US AIDS clinical trials group of the National Institute of Infectious Diseases suggests the use of the subjective peripheral neuropathy screen (SPNS), which is a short self-administered questionnaire on the presence and intensity of three symptoms (*i.e.*, burning and/or

stabbing pain, paresthesia and numbness) of the upper and lower limbs.[65, 66] The brief peripheral neuropathy screen is a tool for the clinical diagnosis of HIV-related neuropathy, which extends the SPNS with a basic physical examination to assess vibration sensation at the big toe and ankle jerk reflex,[67] and is used in many clinical protocols. Quantitative sensory testing has been used in patients with HIV-related neuropathy, and showed lower mechanical pain threshold and static mechanical allodynia and hyperalgesia in patients with pain in comparison with those without pain.[68]

Recommendation 5.2.1. Scales specifically designed to assess pain in Parkinson's disease are lacking (D).

Recommendation 5.2.2. The Toronto Western spasmodic torticollis rating scale is designed to assess the overall severity of cervical dystonia and includes a section for pain assessment, but this scale has not been validated (C).

Recommendation 5.2.3. The brief pain inventory, the Italian pain assessment scale or the neuropathic pain scale are recommended for the assessment of pain in amyotrophic lateral sclerosis, though they are not specific for this condition (C), while caregiver evaluation is recommended if it is not possible to communicate with the patient (D).

Recommendation 5.2.4. The nociception coma scale revised version, and pain assessment in advanced dementia scale are the current gold standard for the assessment of pain in disorders of consciousness and dementia, respectively (C).

Recommendation 5.2.5. Assessment of pain in the previous 24 hours with the numerical rating scale, visual analogue scale, or the verbal rating scale in patients with cognitive dysfunction, should be done daily in oncological patients (D).

Recommendation 5.2.6. HIV-related neuropathy and pain should be assessed with the subjective peripheral neuropathy screen and the brief peripheral neuropathy screen (B), and quantitative sensory testing in selected cases (C).

Question 5.3. What is the impact of pain on neurorehabilitation and how pain can be targeted in this setting in movement disorders, amyotrophic lateral sclerosis, severe acquired brain injury, disorders of consciousness, dementia, oncology and neuroinfectivology?

Parkinson's disease and cervical dystonia

Though pain may be a relatively common non motor symptom in movement disorders and one of the main causes of QoL impairment,[6, 7] the impact of pain on neurorehabilitation of these conditions seems to have received little attention in the literature, and further studies are recommended on this topic.

Amyotrophic lateral sclerosis

Based on recent findings, multidisciplinary rehabilitation has proved effective in managing the complex needs of patients with motor neuron disease, improving QoL by reducing hospitalization and disability.[69] Pain interferes significantly with the activities of daily life,[70] and effective control of pain secondary to immobilization, spasticity and muscle cramps allows patients to undergo continuing physiotherapy and mobilization, preventing tendon retractions and osteoarthritis.[71] Massage can be helpful for trigger-point relaxation, reducing muscle spasms and improving blood circulation to prevent venous stasis.[72]

Severe acquired brain injury, disorders of consciousness and dementia

Any nursing or early rehabilitation that is not accompanied by careful monitoring for the appearance of indirect signs of pain,[58] and if necessary by administration of antalgic therapy in proportion to symptoms, risks activating vicious cycles that could lead to functional setbacks for the patient, such as increase in spasticity or onset of paroxysmal sympathetic hyperactivity.[73] In this phase, the presence of painful symptoms is a potential negative element that can affect rehabilitation efforts, limiting them and/or delaying their effects. In post-acute and chronic phases, the number of potential irritant factors that can cause pain increases, but early appropriate rehabilitation measures can prevent the appearance of secondary damage associated with pain and functional limitation (*e.g.* bed sores, muscle-tendon retraction, frozen joints).

In patients with dementia, the impact of pain reduction during functional recovery cannot be quantified, because rehabilitation outcomes from the current literature are difficult to correlate with pain intensity. In general, however, the impact is positive, although there have been no comparative studies with cogni-

tively competent patients. In particular, antalgic therapy before rehabilitation sessions to reduce incident pain seems beneficial, as in the case of iatrogenic pain before mobilization, medication, and catheterization.[37, 74]

Oncology

Data in the literature indicates that 30-50% of cancer outpatients experience significant pain due to disease progression or therapeutic interventions, with a prevalence of 90% in advanced stages.[75] Given their high vulnerability to adverse and toxic effects of surgery, radiation and chemotherapy treatments, both the central and peripheral nervous systems are considered target structures. Along with other factors, such as young age, recent diagnosis and tumor aggressiveness, pain was significantly associated with a low level of functioning and reduced QoL.[76] Pain interacts with several psychological factors, such as anxiety, depression, distress, emotional instability, sleep disturbances, social isolation/family, thus adversely affecting rehabilitation outcome. Pain along with musculoskeletal problems, deconditioning, fatigue, balance problems, lymphedema and psychosocial issues are likely to be susceptible to rehabilitation.[77] The interaction between pain and disability in oncology is extremely complex, but in the early stages of disease, rehabilitation seems able to provide outstanding functional improvement.[78] The rehabilitation of neurological impairment and pain in (neuro)oncological patients follows the same principles than in other disabling conditions.[79] In patients undergoing surgery for cancer, pain is a major obstacle to functional recovery, and appropriate management seems to have a positive impact on recovery. For other patients, the literature suggests that interference with activities of daily living increases in parallel with increasing pain intensity.[80] It is conceivable that effective pain treatment could improve the functional autonomy of patients, however in the absence of research results, this assumption remains hypothetical and needs confirmation.[81]

Neurological infectious diseases

A few studies demonstrated that higher scores of perceived general health and QoL correspond to better adherence to antiretroviral therapy and reduced access to health resources.

Recommendation 5.3.1. Large studies assessing the impact of pain on quality of life and disability in Parkinson's disease and cervical dystonia are needed (D).

Recommendation 5.3.2. In motor neuron disease, continuing physiotherapy and mobilization prevents tendon retractions and osteoarthritis, and massage can reduce trigger point and muscle spasms, improve blood circulation and prevent venous stasis (GPP).

Recommendation 5.3.3. Pain reduction during rehabilitation of patients with disorders of consciousness and dementia has a beneficial impact on outcome (GPP).

Recommendation 5.3.4. In oncology, although the negative impact of uncontrolled pain on functional autonomy and well-being seems obvious, there have been few studies on this issue and the scientific evidence is not conclusive (GPP).

Question 5.4. Which is the evidence for pain treatment and what is its impact on functional recovery and rehabilitation in movement disorders, amyotrophic lateral sclerosis, severe acquired brain injury, disorders of consciousness, dementia, oncology and neuroinfectivology?

Parkinson's disease

The literature on the treatment of pain in PD, including drug therapy and rehabilitation, is quite limited.[82, 83] In PD, pain may be associated with motor fluctuations, in that it increases in OFF phases and decreases during ON ones.[84] Open-label studies suggest that levodopa may have a positive effect on pain symptoms associated with motor fluctuations.[85] Recently, a randomized controlled trial (RCT) proved the efficacy of rotigotine in the management of pain in PD.[86] The combination of BoNT and physiotherapy was associated to a marked and prolonged control of pain in PD patients with Pisa Syndrome.[87] Other treatments like acupuncture, therapeutic massage and homeopathy seem to have positive effects but have never been tested by RCTs.[88]

Cervical dystonia

It is estimated that more than two-thirds of cervical dystonia patients with painful symptoms require analgesic treatment.[11] RCTs indicate that BoNT may be effective in relieving motor and non-motor symptoms

of cervical dystonia.[89] RCTs of good methodological quality have shown that the combination of BoNT with physical therapy is effective in improving pain control, range of motion, postural control and QoL in cervical dystonia.[90-92] Other approaches requiring more evidence for a stronger recommendation are EMG-biofeedback, electrotherapy, relaxation training, active exercises to improve muscle strength and posture, massage therapy, muscle stretching techniques, mobilization and manipulation techniques for the cervical spine, vestibular stimulation and cognitive-behavioral therapy. Neuromodulation techniques, such as transcranial magnetic stimulation and transcranial direct current stimulation, may be helpful for the treatment of dystonic pain, but controlled studies are lacking.[93] Surgery is used in patients with cervical dystonia when dystonic posture seems refractory to repeated courses of different drug therapies and other interventions. Although several surgical methods are used, the most common one is deep brain stimulation of the globus pallidus internus, but again, controlled studies are lacking.[94]

Amyotrophic lateral sclerosis

The latest Cochrane review on pain therapy in ALS indicates an absence of RCTs or quasi-randomized trials on this topic.[95] Although most patients report pain, this symptom is seldom properly treated, and only three-quarters of ALS patients with pain are treated pharmacologically.[17] The first-line treatments are represented by non-opioid analgesics, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).[17, 19] If response is poor, second-line treatment usually involves opioids,[96] which are also effective in the symptomatic treatment of dyspnea and insomnia.[97, 98] Unfortunately, opioids may depress respiratory function, potentially leading to death, and their use is commonly associated with the terminal phase of the disease.[99] The use of opioids differs in relation to the prescribing physician/service (*i.e.*, neurologist, general practitioner, palliative care service) and to administrative region.[97] For muscle cramps different drugs are used according to the region, namely quinine sulfate (35%), baclofen (19%), phenytoin (10%) and gabapentin in the United States, and quinine sulfate (58%), benzodiazepines (40%), magnesium (25%) and carbamazepine (23%) in Europe.[100] A single open-label study showed some efficacy of levetiracetam for pain in ALS.[101] We found no RCTs on the treatment of spasticity, and the most widely used drug in reference centers were reported to be baclofen (100% of ALS patients with spasticity), followed by tizanidine (36%), dantrolene (29%) and benzodiazepines (21%).[102] In patients with spasticity unresponsive to oral therapy, intrathecal baclofen infusion has been used with good results.[103] *Cannabis sativa* was associated with a reduction of some symptoms, including pain, in a small study based on anonymous questionnaires,[104] but it did not improve muscle cramps.[105]

Severe acquired brain injury, disorders of consciousness and dementia

There is no real agreement on pain treatment in patients with DoC.[106] More evidence of pain perception has been found in patients with MCS than VS, but data on clinical differential diagnosis between VS and MCS shows a percentage error of approximately 40%,[107] and it is advisable to administer pain treatment equally in both conditions. This advice is reinforced by demonstration of voluntary brain activity and hence consciousness in subjects without any voluntary motor or verbal performance, therefore considered clinically unconscious. Treatment should be given especially when behavioral signs suggest pain or when they accentuate in concomitance with nursing manoeuvers or treatment. The principles of pain therapy in such patients follow the general rule of giving priority to treatment of causes, and only then symptomatic treatment (*i.e.*, paracetamol, NSAIDS, opioids) based on criteria of progressiveness and proportionality in relation to the supposed intensity of symptoms and after assessing the risks of interaction or incompatibility with other therapies. In cases of under-treatment, failure to control pain could affect or inhibit the emergence of intentional behavioral responses in patients recovering from disturbances of consciousness,[108] whereas over-treatment could limit cognitive recovery and attention, as well as negatively affect brain plasticity, as suggested by animal studies showing a negative effect of prolonged morphine therapy on cognitive activity.[109] In sABI and DoC patients, behavioral manifestations interpreted as diffuse pain (*e.g.*, psychomotor agitation, opposition to mobilization) [110] can be treated with drugs that raise or regulate the pain threshold, such as GABA-ergic agents (*i.e.*, gabapentin, pre-

gabalin), amitriptyline, and anticonvulsant drugs (*i.e.*, carbamazepine, valproate, oxcarbazepine, lamotrigine, topiramate) and clonazepam. For focal spasticity, infiltration of BoNT has proved effective in reducing pain during nursing and physiotherapy. Intrathecal baclofen infusion has proved effective in reducing pain associated with dystonia and diffuse spasticity, whereas oral baclofen either does not control symptoms or is not tolerated.[111, 112]

The paucity of data on the efficacy of pain therapy in patients with dementia is related to the complex methodology required, as well as the choice of an adequate assessment tool, standardized planning of care, strong team agreement and caregiver involvement. In patients with severe dementia, the efficacy of pharmacological and non-pharmacological pain therapy has been demonstrated by a decrease in personal pain indicators after treatment, which has been used as *ex juvantibus* criterion. It cannot be claimed that psycho-behavioral changes or other clinical signs are expressions of pain unless they are reduced by adequate antalgic therapy, without simultaneous onset or worsening of sedation. The parameter that should be monitored to demonstrate the efficacy of pain therapy is a combination of a standard observational tool with one or more indicators per patient (*e.g.*, face or body expressions, changes in mental status or behavioral/psychic disturbances such as delirium, hallucinations, agitation, aggressiveness, irritability, anxiety, wandering, depression and apathy). Effective diagnosis of pain in severe dementia coincides with successful antalgic therapy. Maintenance of the same level of consciousness than prior to drug (*e.g.*, opioids, tricyclic agents and pregabalin/gabapentin) administration confirms the antalgic effect with no sedation, and requires a simultaneous reduction of psychoactive drugs.[113]

Oncology

The current therapeutic approach to cancer pain is based on the analgesic ladder model proposed in 1986 by the World Health Organization. According to this model, the therapeutic strategy is based on a sequential approach: non-opioid analgesics, NSAIDs and acetaminophen for mild pain (first step), weak opioids (*i.e.*, codeine, tramadol, hydrocodone, etc.) with or without drugs of the first step for mild to moderate pain (second step), strong opioids (*i.e.*, morphine, fentanyl, buprenorphine, oxycodone, methadone, hydromorphone, tapentadol, etc.) with or without drugs of the first level, for moderate to severe pain (third step). For each level, so-called adjuvant drugs, such as anticonvulsants, antidepressants or corticosteroids, can be added. After pain assessment, the patient should be treated starting at the most appropriate level of the analgesic ladder. It follows that major opioids at low doses are permitted as a first choice in opioid-naive patients with moderate/severe pain. Patients with NP should be treated with tricyclic antidepressants and anticonvulsant drugs with careful consideration of their side effects. Shifting from one route of administration to another (*i.e.*, oral, transdermal, subcutaneous, intravenous), as well as opioid administration, is somehow necessary in most patients with cancer pain, including the 10-15% subpopulation that has difficult-to-manage pain. Invasive approaches, such as neuroablative or neuromodulation techniques, are indicated in a small proportion of patients (*i.e.*, 2.7-5.4%). The current indications for invasive treatment are persistent pain, pain refractory to systemic treatments and/or intolerable side effects. Neuroablative procedures (*e.g.*, cordotomy, rhizotomy, etc.) should be reserved for extremely severe pain and patients with reduced life expectancy. In addition to drug therapies, several studies have evaluated the efficacy of adjuvant treatments such as transcutaneous electrical nerve stimulation, but its efficacy on cancer pain is uncertain because evidence is lacking. The effectiveness of complementary and alternative medicine for cancer pain is based on anecdotal observations. Music therapy has been shown to reduce pain intensity with a reduction of opioids, but without statistically significant results.

Neurological infectious diseases

A meta-analysis evaluated a number of drugs for HIV-related NP, but found efficacy only for smoked cannabis, recombinant human nerve growth factor (rhNGF), and topical 8% capsaicin.[114] Among these drugs, only topical 8% capsaicin is approved for NP, while prolonged use of smoked cannabis is not recommended and rhNGF is not available for clinical use. Topical 8% capsaicin seems to offer rapid onset analgesia, long term response and high tolerance.[115] Other agents, which have been tested in high quality RCTs, but proved not effec-

tive in the HIV-related pain include acetyl-L-carnitine, amitriptyline, topical 0.075% capsaicin, gabapentin, pregabalin, mexiletine, peptide T, and lamotrigine. Of note, small RCTs showed efficacy of gabapentin [116] and lamotrigine [117] for pain associated with HIV-related distal sensory peripheral neuropathy. There is limited evidence for the use of non-pharmacological treatments in painful HIV-related neuropathy and no evidence on the effectiveness of physiotherapy. However, some studies showed clinically significant improvements in pain following specific rehabilitation programs. Physical activity is one of the main self-management strategies that might have a favorable impact on outcome of chronic pain, perceived general health and QoL.[118]

Recommendation 5.4.1. The treatment of nociceptive pain in movement disorders, amyotrophic lateral sclerosis, severe acquired brain injury, disorders of consciousness, dementia, oncology and neuroinfectivology should be based on the World Health Organization analgesic ladder (A).

Recommendation 5.4.2. In Parkinson's disease, optimization of antiparkinsonian drugs and rotigotine administration can improve pain (C). Botulinum neurotoxin combined with physical therapy is effective in controlling back pain in Parkinson's disease with Pisa syndrome and in cervical dystonia (B). Neuromodulation techniques and deep brain stimulation have been used to treat pain in dystonia, but further studies are needed on this topic (D).

Recommendation 5.4.3. In patients with amyotrophic lateral sclerosis, opioids are second-line treatments, but may be effective for symptomatic treatment of dyspnea (C). Quinine sulfate, baclofen, phenytoin, gabapentin, benzodiazepines, magnesium, and carbamazepine may be used for muscle cramps (C), and levetiracetam may be considered for refractory patients (D). Tizanidine, dantrolene and benzodiazepines may be used for spasticity (C), and intrathecal baclofen infusion can be considered in refractory cases and diffuse spasticity (D). Self-hypnosis and cannabis can be considered for pain, but the latter does not seem to have an effect on muscle cramps (GPP).

Recommendation 5.4.4. It is advisable to administer pain treatment to patients with vegetative state and minimally conscious state (D).

Recommendation 5.4.5. The efficacy of pain treatment in severe dementia is demonstrated by a decrease in personal pain indicators after treatment, maintenance of the same level of consciousness than prior to drug, and reduction of psychoactive drugs (D).

Recommendation 5.4.6. Switching drug or route of administration may be useful for oncological patients with inadequate pain relief despite escalating doses of systemic opioids (A), and antidepressants or anticonvulsants should be given and side effects should be monitored in those patients with neuropathic pain (A). Neuromodulation and neuroablative techniques should be used for refractory cancer pain syndromes in patients with limited life expectancy (D). The analgesic effect of complementary and alternative medical therapies including music therapy, and transcutaneous electrical nerve stimulation needs confirmation (D).

Recommendation 5.4.7. Topical 8% capsaicin is effective on HIV-related pain (A), and gabapentin and lamotrigine may be effective for pain associated with HIV-related distal sensory peripheral neuropathy (B).

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