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Diagnosis and treatment of pain in plexopathy, radiculopathy, peripheral neuropathy and phantom limb pain. Evidence and recommendations from the Italian Consensus Conference on Pain on Neurorehabilitation.

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Abstract

Pain may affect all aspects of social life and reduce the quality of life. Neuropathic pain (NP) is common in patients affected by plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy. Phantom limb pain (PLP) is a painful sensation that is common after amputation, and its pathophysiological mechanisms involve changes in the peripheral and central nervous system. Given the lack of conclusive evidence and specific guidelines on these topics, the aim of the Italian Consensus Conference on Pain on Neurorehabilitation (ICCPN) was to collect evidence and offer recommendations to answer currently open questions on the assessment and treatment of NP associated with the above conditions and PLP. When no evidence was available, recommendations were based on consensus between expert opinions.

Current guidelines on the assessment and pharmacological treatment of NP can be applied to plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy, while evidence for invasive treatments and physical therapy is generally poor because of the low quality of studies. Treatment of PLP is still unsatisfactory. Data on the functional outcome and impact of pain on neurorehabilitation outcome in these conditions are lacking. In most cases, a multidisciplinary approach is recommended to offer a better outcome and reduce side effects. High quality studies are requested to address the unmet needs in this field.

Keywords: Pain, plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy, phantom limb.

Introduction

Pain may influence mood, sleep, activities of daily life, and social activities, thus reducing the patient's quality of life (Qol) [1]. Neuropathic pain (NP) is caused by a lesion or disease of the somatosensory system [2,3]. Nociceptive pain commonly derives from the involvement of musculoskeletal structures, and biomechanical alterations secondary to neurological diseases [3]. Mixed pain may result from the coexistence of conditions and/or mechanisms of nociceptive and NP [3,4].

Damage to different components of the peripheral nervous system (PNS), including plexopathy, radiculopathy and mononeuropathy, regardless of the etiology, may cause NP that results in disability, reduced participation in daily life activities, impaired QoL [1], and may limit the efficacy of neurorehabilitation procedures. Radiculopathy is frequently associated with mixed pain, because of the coexistence of NP secondary to radicular damage and nociceptive pain deriving from osteoarticular structures, such as intervertebral disc, facets, joints, or ligaments [5]. The large number of underlying etiologies, the variety of clinical features and neurophysiological changes, as well as the biopsychosocial variables, may cause a delay in diagnosing pain in PNS diseases, thus facilitating pain chronification, which in turn may reduce the therapeutic response [6].

Phantom limb pain (PLP) is the subjective experience of persistent painful perception of a physical segment of the body after its amputation. New findings on its underlying neurophysiological mechanisms changed the view of PLP from a psychogenic phenomenon and/or a PNS condition to a process where central nervous system plasticity plays a key role, offering new premises for neurorehabilitation approaches, despite the treatment of this condition is still debated [7].

The aim of the Italian Consensus Conference on Pain on Neurorehabilitation (ICCPN) is to collect evidence and offer recommendations to answer open questions on the assessment and treatment of pain conditions that can be addressed in the neurorehabilitation setting and to fill the knowledge gap with expert opinions, when no evidence is available. Here we will address pain associated with PNS diseases and PLP.

Materials and Methods

The full methodology of the ICCPN is described in details elsewhere [8]. The strength of recommendations was scored according to a scale from A to good practice point (GPP) and is reported in parentheses after each recommendation [8]. We systematically searched Pubmed and Embase using the keywords pain, neuropathic pain, peripheral neuropathy, plexopathy, radiculopathy, mononeuropathy, methods, evaluation, pain assessment, measurement, standardized criteria, classification, definition, predictive factors, drug, (pharmacological) therapy/treatment, surgical treatment, rehabilitation, physical therapy carpal tunnel syndrome, ulnar nerve entrapment, tarsal tunnel syndrome, predictors, amputation, amputees, phantom limb, corresponding MeSH when available, and all the possible combinations of these keywords for original research studies published from 1993 to 2013, and from 1983 to 2013 for papers on treatment. Later on, the search was updated to 2015 and some selected papers were added to the review. A consensus was reached to obtain recommendations from current evidence, and expert opinion when no evidence was available.

Results and Recommendations

Question 6.1. What are the main characteristics of pain in plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy and phantom limb pain.

Plexopathy, radiculopathy and mononeuropathy. NP represents the most common type of pain in plexopathy, radiculopathy, and mononeuropathy. Patients with radiculopathy, however, may experience mixed pain, where nociceptive pain secondary to disc herniation, facet joint disease, and other osteoarticular conditions may coexist with NP. NP is described as lancinating, stabbing, or shooting, with the possible presence of hyperalgesia to thermal and punctate stimuli and allodynia to mechanical stimuli [9]. Paroxysmal pain, allodynia and constant spontaneous pain are frequently reported in carpal tunnel syndrome [10]. It should be kept in mind, however, that pain descriptors cannot consistently separate nociceptive from NP [11].

Peripheral neuropathy. Pain is frequently described in peripheral neuropathy. A recent research trend is to characterize the NP sensory profile in PNS diseases to collect information on NP pathophysiological mechanisms regardless of etiology [12]. This psychophysical approach is aimed to better target NP therapy in the single patient [13], but has not yet resulted in a stratified treatment approach to NP [14]. A large observational study, using the NP screening tool PainDETECT, found burning and prickling pain with numbness to represent the most common cluster (i.e., 26% of cases) in patients with painful diabetic neuropathy (PDN) [15]. A descriptive study to characterize the NP sensory profiles with the neuropathic pain symptom inventory (NPSI) showed that patients with diabetic or HIV-related painful polyneuropathy reported more severe burning or pinprick sensation, electric shock, stabbing pain, and

tingling than those suffering from post-traumatic mononeuropathy [16]. A prospective multicenter study on immune-mediated neuropathies showed that paresthesia and dysesthesia are more common in chronic inflammatory polyradiculopathy and anti-MAG neuropathy, burning spontaneous pain is more frequently reported in vasculitis neuropathy, and patients with Guillain-Barre syndrome and multifocal motor neuropathy complain of pressure spontaneous pain [17]. Another prospective study confirmed some of the results reported above, and found that paresthesia and dysesthesia were more common in cryoglobulinemic, diabetic, hereditary, and idiopathic neuropathy, while PHN patients complained paresthesia, dysesthesia and superficial spontaneous pain [18].

Phantom limb pain. Approximately 75% of amputees report PLP [19]. Different mechanisms have been suggested to explain the genesis and maintenance of PLP, including peripheral phenomena (e.g., neuroma formation), spinal (e.g., changes in GABAergic receptor function), and brain changes (e.g., plasticity in the cortical representation of the stump, involvement of the corpus callosum), and psychogenic mechanisms [20,21]. PLP usually begins in the first few days after amputation, and in most cases the pain becomes chronic, with a high variability in terms of frequency, intensity and quality of pain sensation [22].

Recommendation 6.1.1. Nociceptive and neuropathic pain may coexist in patients with plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy and phantom limb pain (GPP).

Recommendation 6.1.2. Most patients with plexopathy, radiculopathy, and mononeuropathy report lancinating, stabbing, shooting pain, hyperalgesia or allodynia, and those with peripheral neuropathy frequently complain of

paresthesia, dysesthesia or spontaneous deep pain (C). Screening and assessment tools for neuropathic pain should not be used alone but as a part of a diagnostic algorithm including history, examination and confirmatory tests (B). Recommendation 6.1.3. Phantom limb pain becomes chronic, with a high variability in terms of frequency, intensity and qualities and descriptors of pain.

Question 6.2. Are there methods or standardized criteria for the assessment of pain in plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy and phantom limb pain?

As discussed above, patients with plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy, and phantom limb pain may experience neuropathic, nociceptive or mixed pain. The definition of these three types of pain, and the clinical and instrumental tools to separate them have been discussed in details in another ICCPN paper [3]. The grading system of the International Association for the Study of Pain Special Interest Group on Neuropathic Pain (NeuPSIG) indicates three levels of diagnostic certainty for NP, namely possible, probable and definite [2,22]. Possible NP requires a) a relevant neurological lesion or disease in the patient's history and b) a neuroanatomically plausible distribution of symptoms [2,22]. A close temporal relationship between the lesion or disease and the appearance of pain may strengthen the clinical suspicion of neuropathic pain. Probable NP is based on c) confirmation of negative or positive sensory signs in the pain distribution during the examination of the patient [23]. The definite level of certainty requires confirmation of the lesion or disease of the somatosensory nervous system by an objective diagnostic test [2].

The NeuPSIG grading system represents the current *gold standard* for the diagnosis of NP, because of the absence of other diagnostic algorithms, or biological markers for NP, but it requires solid notions of the PNS anatomy and is based on a neurological approach that may appear unusual to other medical disciplines [2,3]. The variability of innervation territories among single individuals, and the extraterritorial spread of symptoms secondary to central sensitization may make deciding whether pain has a neuroanatomically plausible distribution tricky [3,23].

NP screening tools and questionnaires, which have been proposed to facilitate the recognition of NP [24], include the Leeds assessment of neuropathic symptoms and signs [25], the neuropathic pain questionnaire [26], the *douleur neuropathique en 4 questions* (DN4) [27], the PainDETECT [28], and the ID-Pain [29]. The NP screening tools share a short time of administration and a good sensitivity/specificity profile, and a few questions on pain characteristics combined with a very simplified examination [4,24]. The characteristics of the NP screening tools, and their sensitivity and specificity were reported in details elsewhere [3]. However, they are not reliable in about 10-20% of NP patients, and should guide further diagnostic steps, but should not replace the NP grading system. When choosing a NP screening tool, the presence of a validated translation in the native language of the patient should be considered, and, to date, DN4 is the only one with a validation in Italian language [30].

Pain intensity may be assessed with the numerical rating scale (NRS), the visual analogue scales (VAS), the verbal rating scales (VRS), and the Gracely pain scale, which is a combination of VAS and VRS [31]. Pain quality and temporal features can be evaluated with the McGill pain questionnaire (MPQ) and its 15-items short form. MPQ

and and its 15-items short form are generic pain questionnaires, which are not specifically validated but frequently used for the assessment of NP [32]. Specific scales to assess qualities and temporal features of NP include the neuropathic pain scale (NPS) [33] and the NPSI [34]. Italian versions exist for NPS and NPSI [35,36]. QoL may be measured with a generic scale, such as the SF-36 [37]. Tampa scale of kinesiophobia (TSK) may be used to evaluate fear of movement [38].

Instrumental tools that are commonly used in the assessment of pain in plexopathy, radiculopathy, mononeuropathy, and peripheral neuropathy, and their advantages and limitations, have been dealt in more details in another ICCPN article [3]. Nerve conduction study (NCS) and needle electromyography (EMG) are used to define the site of PNS injury (i.e., nerve root, plexus, nerve trunk), explore the involvement of motor and/or sensory fibers, offer information on the type of nerve damage (i.e., axonal, demyelinating), give hints on the underlying etiology [39]. Quantitative sensory testing, laser evoked potentials, and skin biopsy may assess the function of small nerve fibers, and have been used in therapeutic studies [3,40].

Plexopathy, radiculopathy and mononeuropathy. Clinical evaluation is the basis for the characterization of NP in these conditions. The evaluation of patients with cervical or lumbar radicular pain requires very careful history collection and an accurate neurological examination, focused on pain location and its characteristics [5]. Pain radiating to the lower limb in a dermatomal fashion is traditionally considered a good clinical marker of nerve root compression secondary to lumbar disc herniation [41], but this point is quite debated, because nociceptive pain originating from the spine and/or sacroiliac joint with no nerve damage may spread to the lower limb in a sciatica-like

fashion [42]. The discrepancy between clinical sciatica and disc herniation level on magnetic resonance imaging (MRI) was found not to be rare [43]. Moreover, a systematic review reported important variations in the test-retest reliability of pain location and distribution across different test-retest scenarios and across body regions [44]. Despite their wide use in everyday clinical practice, the diagnostic accuracy of the test of Lasègue or straight leg raising test, the cross straight leg raising test and related maneuvers is limited by its low specificity [45]. Limitations of the test of Lasègue and related tests include poor standardization, low intra and interobserver reliability, and the influence of age, gender, diurnal variation, and psychosocial factors. Single tests of the clinical examination are reliable and have acceptable diagnostic properties for cervical radiculopathy, but applying more tests may be more useful than any single test [46]. Needle EMG has good intrarater but low interrater reliability and moderate diagnostic accuracy and modest specificity for radiculopathy [47]. Neuroimaging, either MRI or computerized tomography scan, is very sensitive in detecting disc herniation, but has low specificity and a very high likelihood of false positive findings even in a significant number of asymptomatic persons [48]. Studies comparing the diagnostic value of clinical examination, needle EMG and neuroimaging, either alone, or in combination, for recognizing radiculopathy are lacking. There is limited evidence for the accuracy of selective nerve root injections as a diagnostic tool for evaluating low back pain with radicular features [49]. Ultrasound and MRI are helpful for the assessment of nerve damage, especially in traumatic lesions, but they are available only in specialized centers.

Peripheral neuropathy. Studies on the assessment of NP in peripheral neuropathy are scarce. Clinical evaluation should include examination of superficial and deep sensation, motor signs, and tendon reflexes, a NP screening tool, NRS or VAS for measuring pain intensity, a specific scale for NP assessment, such as the NPS or the NPSI [33-36], a QoL questionnaire [37], and/or the TSK [38]. Among screening tools, DN4 demonstrated good diagnostic accuracy in identifying the presence of PDN, with 80% sensitivity and 92% specificity [4,30,50]. Instrumental evaluation should include NCS and needle EMG to get a definite diagnosis of peripheral neuropathy, explore its extent, and offer information on the type of nerve damage. Quantitative sensory testing, laser evoked potentials, sural biopsy, and skin biopsy do not represent routine tests for neuropathy, but they may be helpful in small fiber neuropathy, or difficult cases. Nerve ultrasound is a useful diagnostic tool to assess morphological changes in peripheral neuropathy, to complement information from clinical assessment and NCS. Laboratory tests to explore the etiology of peripheral neuropathy should be performed as needed.

Phantom limb pain. The VAS, NRS, and MPQ are the most widely used rating scales to measure PLP intensity. The Brief Pain Inventory, a multidimensional scale investigating pain intensity and its interference on everyday life, can be used in PLP. The prosthesis evaluation questionnaire investigates the phantom non-painful sensations [51], and may be useful in this condition.

Recommendation 6.2.1. A multimodal evaluation including clinical examination, electrodiagnosis and neuroimaging is helpful for the assessment of pain in plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy, and phantom limb pain. In addition to scales for measuring pain intensity, screening

tools for neuropathic pain, and questionnaires for neuropathic pain qualities and quality of life should be used. Measures of phantom limb pain intensity should score the mean and the worst pain occurring for at least one week (GPP).

Question 6.3. Are there any predictive factors for the development of pain or its outcome in plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy and phantom limb pain?

Plexopathy, radiculopathy and mononeuropathy. Most of the studies we found were on brachial plexopathy, likely because of its frequent occurrence in young people, the severity of pain, and the functional impact. In traumatic and iatrogenic brachial plexopathy, the intensity of pain appears to be related to the extension of nerve damage and the number of avulsed nerve roots [52]. Block of the nonavulsed roots with local anesthestics can reduce pain, suggesting that their damage may also contribute to pain in traumatic brachial plexus injury [53]. Local inflammation and the release of neurotrophic factors lead to scar formation and neuroma development. Therefore, early surgery on the root or neuroma may result in pain improvement [54]. On the other hand, the release of neurotrophic factors may lead to pain chronification in a minority of patients who underwent nerve root grafting [54]. Another predictive factor for pain is the time elapsed between brachial plexus injury and surgery, in that early repair was found to be more effective than delayed intervention in pain relief and functional recovery [55]. Data on predictive factors for pain associated with radiculopathy are inconclusive and blurred by poor definition of radicular pain, and the frequent coexistence of low back pain of nociceptive or uncertain origin. It should be underlined that acute radicular pain

ameliorates in a few weeks or months in the large majority of patients. Previous reports indicated that psychosocial factors, depression, clinical signs, sensory pain descriptors can predict postoperative pain after lumbar discectomy, but these findings need further confirmation [56].

The search on mononeuropathy retrieved no conclusive findings.

Peripheral neuropathy. Most studies on predictors for the development of pain come from diabetic neuropathy. A cross-sectional study in patients with diabetes mellitus identified advanced age, type 2 diabetes, other diabetic complications, history of foot ulcers, high cholesterol and triglyceride levels, alcoholism, and high values of body mass index (BMI) as predictive factors for NP [57]. In a previous cross-sectional study, BMI was confirmed as the only independent clinical parameter predictor for PDN together with the severity of sensory deficits [50,58]. A prospective study of patients with herpes zoster identified cigarette smoking, previous trauma or surgery at the herpes zoster area as predictive factors for pain intensity and persistence [59].

Phantom limb pain. The presence of pre-amputation pain increases the risk of PLP after three months [60]. Similarly, pre-amputation pain intensity predicts acute pain during the first week post-surgery and chronic PLP after two years [61]. Other factors that were reported to predict PLP include cause of amputation, prosthesis use, years elapsed since amputation, bilateral amputation, and lower limb amputation [62]. The presence of depressive symptoms was found to be a common predictor of increased level of intensity and bothersomeness of PLP, residual limb pain, and back pain in amputees [63].

Recommendation 6.3.1. The extension of damage, the number of avulsed roots, the presence of neuroma, and the time that elapses between trauma and surgery are predictive factors for pain in traumatic lesions of the brachial plexus (C).

Recommendation 6.3.2. Body mass index (B), age (C) and the severity of sensory deficits (C) are predictors for painful diabetic neuropathy.

Recommendation 6.3.3. Pain prior to amputation is the best predictor for phantom limb pain (B).

Question 6.4 What is the impact of pain in patients undergoing rehabilitation for plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy and phantom limb pain?

Plexopathy, radiculopathy and mononeuropathy. Sciatic pain significantly increases disability and worsens self-reported mental health status although the large majority of patients ameliorate within the first year after pain onset [64]. Pain in patients with radiculopathy may be associated with reduced cervical and lumbar range of motion, but the specific impact of radicular pain is undetermined because of the coexistence of cervical and low back pain.

Peripheral neuropathy. We could not find data on this topic. Reasons for this lack of evidence may include the variable etiology of peripheral neuropathy, and the presence of a 'double disability' resulting from pain itself and the underlying disease, where the specific impact of the two conditions on physical and psychosocial function cannot be separated [65].

Phantom limb pain. There is no evidence that the reduction of PLP can improve functional outcome, but PLP is associated with depressive symptoms that, in turn, may reduce treatment efficacy, function and QoL [66]. High PLP intensity has a negative impact on activities of daily life [19], use of prosthesis, mobility, and social participation [67].

Recommendation 6.4.1. The impact of pain on neurorehabilitation procedures and outcome should be assessed in patients with plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy, and phantom limb pain (GPP).

Recommendation 6.4.2. Phantom limb pain reduces quality of life and can cause depression (C) that should be treated (GPP).

Question 6.5. What is the evidence for pharmacological and non-pharmacological treatments of pain in patients with plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy, and phantom limb pain?

Evidence from randomized controlled trials (RCTs) on pharmacological treatments for NP mainly derives from patients with PNS conditions, and in particular PDN and post-herpetic neuralgia. Based on the evidence from these RCTs, guidelines on the pharmacological treatment of NP have been published [68-73]. These guidelines, which have been dealt in more details in another ICCPN article [74], converge to a good extent on which drugs should represent first, second and third-line for NP. In particular, the recent NeuPSIG guideline, which addressed some important methodological issues, indicate that tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, α2-δ ligands (i.e., pregabalin and gabapentin) should be first-line treatment, 5% lidocaine

patch, 8% capsaicin patch, and tramadol represent second-line, and strong opioids and botulinum neurotoxin should be used as third-line for NP, with lidocaine, 8% capsaicin patch and botulinum neurotoxin type A to be used for peripheral NP only [73,74]. The choice among first line drugs should take into account comorbidities, and regular follow-up is needed to monitor response to treatment and adverse events [74]. Because of the large number of non-responders to drugs for NP, including first-line ones, some drug combinations (e.g., α2-δ ligands plus opioids, α2-δ ligands plus tricyclic antidepressants, α2-δ ligands plus duloxetine), can be considered [74-77], but there is no conclusive evidence on a superiority of combination treatment on monotherapy and on which specific drug combination should be preferred [78]. Despite their wide use, oral nonsteroidal anti-inflammatory drugs (NSAIDs) appear to be not effective in NP [79].

Whether and to what extent overall evidence and guidelines on NP should be directly translated to plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy, and phantom limb pain remains undetermined. However, we suggest that NP guidelines should be used when approaching these patients, taking into account the evidence that is specific to each of these conditions and will be presented below.

Plexopathy. Pharmacological studies on treatment of pain in plexopathy are few and low-quality ones. A recent meta-analysis yielded inconclusive evidence on the use of immunotherapy in idiopathic lumbosacral plexopathy, because of the lack of RCTs [80]. As discussed above, early surgery for neuroma after traumatic brachial plexopathy may ameliorate pain [54]. More invasive surgical procedures may be considered in the most severe cases [81].

Radiculopathy. Epidural and/or peridural injection of corticosteroid and local anesthetic is commonly used for radicular lumbosacral pain, despite the small and short-term benefit and the evidence that corticosteroid does not offer additional benefit in comparison to local anesthetic alone [74,82-84]. Evidence on physical therapy for pain associated with radiculopathy is lacking, because of the methodological issues and the poor quality of the studies, but it may be considered as an adjunctive option in patients that have side effects to pharmacological treatments [74]. There is no evidence on which are the best timing of surgery and type of surgical procedure in NP secondary to radiculopathy [85].

Carpal tunnel syndrome. Surgical median nerve release is considered the treatment of choice for carpal tunnel syndrome (CTS), but there is neither evidence nor consensus on the most effective surgical technique and its timing [86]. There is only limited, short-term or no evidence for a number of non-surgical interventions, including oral steroids, steroid injections, vitamins, ultrasound, electromagnetic field therapy, nocturnal splinting, ergonomic keyboards, exercise and mobilisation interventions in CTS patients [87-90].

Ulnar nerve entrapment at the elbow. Two systematic reviews reported insufficient evidence to identify the best surgical treatment for cubital tunnel syndrome, but a trend towards better outcome with transposition of the ulnar nerve as opposed to simple decompression [91,92].

Tarsal tunnel syndrome. Management of this entrapment neuropathy remains a challenge, but excellent results may be achieved with nerve decompression in selected patients [93]. Steroid injection may cause damage to the tendon of the tibialis posterior

muscle. Conservative approach may include rest, physical therapy, ice, heat, ultrasound, and the use of orthoses, but evidence on these treatments is lacking.

Peripheral neuropathy. Most of the studies on painful peripheral neuropathy come from PDN, because of its epidemiological relevance, and the frequent presence of pain in comparison to other peripheral neuropathies. Despite the availability of guidelines on NP treatment [74,94], use and doses of evidenced-based NP-related medications in patients with painful peripheral neuropathy was found to be low, and lower than the use of NSAIDs that have no proven efficacy for this condition, suggesting possible sub-optimal NP management among these patients [95,96]. Furthermore, the drugs with proven efficacy in RCTs fail and/or cause side effects in a consistent number of patients, and the availability of new drugs allows a wider choice, but does not invariably translate into the achievement of higher patient's satisfaction [97]. Thus, despite the increased number of drugs that were found to be effective for NP in the last years, unmet needs remain in the field of pharmacological treatment of peripheral NP.

Most of the studies on non-pharmacological treatments in peripheral NP are in patients with PDN, while evidence from other peripheral neuropathies is scarce or absent. Transcutaneous electrical nerve stimulation (TENS) should be considered in the treatment of PDN, but the effect is short-lasting and hindered by a consistent placebo effect, and there is little evidence to support its long-term effect [98,99]. A RCT showed that transcutaneous frequency-modulated electromagnetic neural stimulation is a safe treatment for symptomatic diabetic neuropathy, with immediate, although transient, reduction of pain, and no effect on nerve conduction velocity [100]. Acupuncture [101] and physical exercise [102] might be considered, while data for magnetotherapy are

conflicting [103], and there is no evidence for the use of photon stimulation and low level laser therapy in PDN [104,105].

Phantom limb pain. In clinical practice, the management of PLP often involves a combination of drugs with proven evidence for NP (e.g., anticonvulsants, antidepressants, local anesthetics, opioids), NSAIDs, N-methyl D-aspartate receptor antagonists, and calcitonin in order to target multiple pathophysiological mechanisms but the best pharmacologic management for PLP is undetermined [106]. The short- and long-term effectiveness of these drugs for clinically relevant outcomes that include pain, function, mood, sleep, quality of life, satisfaction and adverse effects remains unclear because of the small number of studies with limited sample size, and lack of long-term efficacy and safety outcomes [107]. Morphine, gabapentin and ketamine demonstrate trends towards short-term analgesic efficacy, while memantine and amitriptyline were ineffective on PLP, and trials on calcitonin, local anesthetics and dextromethorphan yielded inconclusive findings [107,108]. Because of the uncertain evidence of efficacy, and small increased risk of cancer associated with long-term use, we recommended to avoid calcitonin in PLP patients. Some reports suggested the perioperative treatment of PLP by blocking the afferent barrage with local anaesthetics and/or opiates [108], but these findings were not confirmed in a RCT exploring epidural block with bupivacaine and morphine started before the amputation and continued into the postoperative period [109]. Contralateral lower limb myofascial injection with local anaesthetic was found to reduce PLP in a single exploratory placebo-controlled study [110], but these data were not confirmed.

It has been hypothesized that projecting TENS sensation into the phantom limb might facilitate perceptual embodiment of prosthetic limbs [111]. The published literature on the effectiveness of TENS for the management of PLP and stump pain lacks the methodological rigour and robust reporting needed to confidently assess its effectiveness [112]. Data on acupuncture for PLP are not conclusive because of the low quality of the reports.

It has been reported that mirror therapy, i.e., reflection of the unaffected limb in a mirror serving as a virtual representation of the missing limb, may be associated with PLP reduction [113]. Mental imagery, mental practice and phantom exercises are based on the imagination of moving the missing limb and aimed to inhibit motor cortical reorganization that occurs after amputation [114]. A recent RCT showed that progressive muscle relaxation, mental imagery, and phantom exercise training significantly reduce PLP and sensation [115].

Non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation, may modulate abnormal cortical plasticity and can temporarily relieve pain in some patients with chronic NP, but data on their application for PLP are only preliminary [116].

Recommendation 6.5.1. Current therapeutic guidelines on the treatment of neuropathic pain, which indicate a) tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, pregabalin, and gabapentin as first-line, b) 5% lidocaine patch, 8% capsaicin patch, and tramadol as second-line, and c) strong opioids and botulinum neurotoxin as third-line (A), should be applied to plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy, and

phantom limb pain, considering the specific evidence for each of these conditions (GPP).

Recommendation 6.5.2. Combination therapy among first-line drugs for neuropathic pain may be more effective and/or associated with less side effects than single drugs, and can be considered in patients with plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy, and phantom limb pain (GPP).

Recommendation 6.5.3. Epidural and peridural injection of corticosteroid and local anesthetic, physical therapy, and surgery can be considered for pain associated with radiculopathy in patients with no response and/or side effects to pharmacological treatments (GPP).

Recommendation 6.5.4. Surgical median nerve release should be considered the treatment of choice for carpal tunnel syndrome, but there is no evidence or consensus on the most effective surgical technique and best timing (GPP). Non-surgical interventions can be considered in carpal tunnel syndrome (GPP).

Recommendation 6.5.5. In patients with painful diabetic neuropathy transcutaneous electrical nerve stimulation can be considered, but its effect is short-lasting and hindered by a consistent placebo effect (B), physical exercise may be useful (C), while evidence is preliminary for acupuncture (D).

Recommendation 6.5.6. In patients with phantom limb pain morphine, gabapentin and ketamine can have short-term analgesic effect (B), amitriptyline is not effective (B), and calcitonin should be avoided (GPP), while there is conflicting evidence on the role of epidural blocks (C). Non-pharmacological treatments that

can be considered for phantom limb pain include mirror therapy, mental imagery, phantom exercises, progressive muscle relaxation, and non-invasive brain stimulation (GPP).

Question 6.6. What is the impact of pain treatment on functional recovery and neurorehabilitation outcome in patients with plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy, and phantom limb pain?

Data on the influence of pain treatment on functional recovery and rehabilitation outcome in these conditions are scanty. NP worsens gait parameters and increases the risk of falling in patients with polyneuropathy [117,118], but whether treating pain may significantly ameliorate walking abilities is unclear. Pain is one of the main symptoms to be addressed with a multidimensional approach in the rehabilitation of brachial plexus lesions, because it may influence the rehabilitation outcome [119]. It may be hypothesized that effective treatment of pain may have benefits for neurorehabilitation outcomes, but future studies should further address this point.

Recommendation 6.6.1. The effect of pain treatment on functional recovery and rehabilitation outcome in patients with plexopathy, radiculopathy, mononeuropathy, peripheral neuropathy and phantom limb pain should be assessed as potentially relevant.

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