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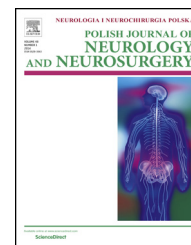
Review article

Diagnosis and management of neuropathic pain: Review of literature and recommendations of the Polish Association for the Study of Pain and the Polish Neurological Society – Part Two

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ABSTRACT

Neuropathic pain may be caused by a variety of lesions or diseases of both the peripheral and central nervous system. The most common and best known syndromes of peripheral neuropathic pain are painful diabetic neuropathy, trigeminal and post-herpetic neuralgia, persistent post-operative and post-traumatic pain, complex regional pain syndrome, cancer-related neuropathic pain, HIV-related neuropathic pain and pain after amputation. The less common central pain comprises primarily central post-stroke pain, pain after spinal cord injury, central pain in Parkinson disease or in other neurodegenerative diseases, pain in syringomyelia and in multiple sclerosis.

A multidisciplinary team of Polish experts, commissioned by the Polish Association for the Study of Pain and the Polish Neurological Society, has reviewed the literature on various types of neuropathic pain, with special focus on the available international guidelines, and has formulated recommendations on their diagnosis and treatment, in accordance with the principles of evidence-based medicine (EBM). High quality studies on the efficacy of various

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Persistent post-operative and
post-traumatic pain
Malignant pain
HIV-associated neuropathic pain
Central pain

medicines and medical procedures in many neuropathic pain syndromes are scarce, which makes the recommendations less robust.

1. Post-herpetic neuralgia

1.1. Diagnosis

Post-herpetic neuralgia (PHN) is the unilateral pain located within dermatomes affected by viral infection, persisting or recurring more than 3 months after the onset of herpes zoster infection and after the healing of skin lesions. It occurs in 9–15% of patients who have suffered from herpes zoster [41,105].

Pain in PHN may be persistent or paroxysmal; it has burning, stinging, throbbing or sharp and shooting quality, resembling stabbing or electric shock. Usually, it increases in the evening and at night. It is exacerbated by cold rainy weather and stress. Examination reveals sensory abnormalities including allodynia, hyperalgesia and hyperesthesia.

The risk factors for PHN include: age, female sex, severe pain before the onset of rash, location within the first branch of the trigeminal nerve, involvement of dermatomes not adjacent to each other, diabetes, history of cancer or other immune compromising diseases and very severe acute phase of the disease with intense pain as well as involvement of multiple dermatomes. Pain may resolve spontaneously within a few months, but in some patients it persists for years or even for life [61,105].

1.2. Treatment

Efficacy of a live attenuated virus vaccine (Zostavax) has been demonstrated for the prevention of zoster and PHN (the incidence of zoster reduced by 61.1% and the risk of PHN development reduced by 66.5%) [83]. The use of an antiviral drug (acyclovir) up to 48 h after the onset of skin lesions limits the viral proliferation in structures of the nervous system and reduces the incidence of PHN. The incidence of PHN is also reduced by effective pain management in the acute phase of the disease with the use of non-opioid analgesics, weak or strong opioids, sympathetic nerve blocks, intravenous infusions of lidocaine as well as antidepressants and anticonvulsants [12].

Recent systematic review and a meta-analysis of 28 studies evaluating the efficacy of 20 different drugs in over 4000 patients with PHN concluded that nearly all of these drugs were superior to placebo; the best evidence on the efficacy was provided for pregabalin, gabapentin, 8% capsaicin and amitriptyline. Of treatment studied in more than 50 patients, the greatest pain reduction has been achieved with opioids, while pregabalin at a daily dose of at least 300 mg was the most effective drug to achieve 30% or 50% reduction in pain [100].

The recommendations for PHN treatment, including those prepared by the International Association for the Study of Pain (IASP) [38] and the European Federation of Neurological Societies (EFNS) [5] experts, have been published recently and were quite consistent. According to them, the drugs with the level A evidence include: 8% capsaicin, gabapentin, pregabalin, 5% lidocaine patches, opioids (morphine, oxycodone, and methadone) and tricyclic antidepressants (TCAs) (amitriptyline, desipramine and nortriptyline – the last two are not available in Poland).

Management of a patient with PHN depends on the type of pain reported. If allodynia or hyperalgesia predominate topical treatment is recommended (patches with 5% lidocaine or 8% capsaicin), as well as infiltration anesthesia with 1% lidocaine and sympathetic nerve blocks in the area of pain. Otherwise, pregabalin, gabapentin and TCAs are recommended, as they effectively alleviate spontaneous pain with burning components and paresthesias. Opioids are recommended for pain of high intensity [5,6,38,39,76].

Similarly to the other types of neuropathic pain, management should start with monotherapy. Alternative monotherapy ought to be tried, if the first-choice drug fails. If monotherapy is ineffective, combined pharmacotherapy is possible (e.g. an anticonvulsant with an antidepressant, 5% lidocaine with an anticonvulsant and an antidepressant, or 5% lidocaine with an anticonvulsant, an antidepressant and an opioid) [23].

Sympathetic nerve blocks are used in some centers despite the lack of evidence for their efficacy. The efficacy of blocks is the higher, the earlier it is used, which may result from inhibition of response resulting from hypersensitivity of damaged axons or their endings to released noradrenaline [26,40,111].

Other non-pharmacological methods, such as acupuncture, transcutaneous electrical nerve stimulation (TENS), laser therapy, topical cooling or spinal cord stimulation, may also be used in some cases refractory to physical therapy and pharmacotherapy [4].

1.3. Recommendations

1. PHN may be diagnosed in individuals suffering from unilateral pain located in dermatomes in which acute lesions caused by the zoster virus have occurred. PHN may be diagnosed after the complete healing of these lesions.
2. Among many drugs of proven efficacy, the following are recommended as a first-line therapy: pregabalin, gabapentin, 8% capsaicin, 5% lidocaine patches, amitriptyline and opioids.
3. The choice of the first drug should be based on the intensity and type of pain as well as comorbidities.
4. If subsequent monotherapies fail, it is possible to use a combination of drugs from different therapeutic groups.

2. Complex regional pain syndrome

2.1. Diagnosis

Complex regional pain syndrome (CRPS) is a particular type of neuropathic pain affecting distal part of an upper or lower limb. Two forms of this syndrome have been distinguished: type I (reflex sympathetic dystrophy, RSD) without confirmed peripheral nerve injury and type II (causalgia) with concomitant peripheral nerve injury. The incidence of CRPS-I is assessed at 5.5/100,000 and of CRPS-II at 4.5/100,000.

Pathological lesions in CRPS occur at many levels of the nervous system involved in nociception, and they result in sensory, motor and autonomic disturbances within a limb affected by pain. The syndrome is triggered by a noxious stimulus acting peripherally, often a slight injury or immobilization of peripheral part of a limb. The signs of CRPS are usually limited to one limb or its part, but they can spread to other limbs. Usually, pain is accompanied by peripheral sensory disturbances, mild weakness and other motor disturbances, as well as swelling, vasomotor dysfunction and other autonomic lesions. Involuntary movements, such as tremor or dystonia, are observed in some patients. Patients suffering from CRPS often experience anxiety, depression, pain catastrophizing, pain behaviors, focusing on signs, and fear of the consequences of disease.

The recently published criteria for CRPS diagnosis introduced a list of typical symptoms and signs assigned to four categories of disturbances: positive sensory, vasomotor, sudomotor/edema, as well as motor/trophic disturbances. According to these criteria, CRPS may be diagnosed in clinical practice based on the presence of at least one symptom in at least three of the abovementioned categories and at least one sign in at least two categories [53].

2.2. Treatment

Due to the complex nature of its occurrence, CRPS is very difficult to treat. None of the medicines or non-pharmacological methods of treatment achieved level A evidence. So far, only lamotrigine, TCA and opioids have been shown to be effective in single randomized or other large case-series (grade B). In practice, various methods of physical therapy, psychotherapy, local anesthesia techniques, neuromodulation and pharmacotherapy are used in the treatment of this syndrome. Comprehensive rehabilitation is the basis for therapy, and multidirectional, integrated treatment is aimed at the restoration of limb function. The choice of intervention in a given case depends on the type and severity of symptoms. Vitamin C at a dose of 500 mg/day may be effective in the prophylaxis of CRPS, as documented by a study among patients after wrist fracture [115].

Physical therapy should be initiated as soon as possible. Intensity of procedures should be tailored individually to the limit of pain. Procedures perceived as painful may cause deterioration. There are no studies that might help to identify which method of physical therapy would be the most effective for a given patient [71,75]. Occupational therapy aimed at the improvement of limb functioning is especially recommended in the case of CRPS with symptoms in the upper limb [81].

Psychotherapy is recommended in the cases where psychological or psychiatric examination reveals mental disorders which may be responsible for the occurrence or persistence of pain. However, there is no evidence confirming the efficacy of different forms of psychotherapy [13,30,54,71]. The use of analgesics according to the WHO scheme is recommended; there are no controlled trials to support that notion, however. This applies to non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, as well as weak and strong opioids. Non-steroidal anti-inflammatory drugs or paracetamol may be given to patients with pain of low or moderate intensity. Tramadol, being effective in many other neuropathic pain syndromes, may also be used in CRPS. Despite the fact that there is no evidence on efficacy, many experts consider opioids to be one of the basic elements of multidirectional treatment of severe CRPS not responding to other forms of treatment [54,56]. Prednisolone 30–40 mg/d was given orally in the acute phase of CRPS, decreasing the intensity of disease symptoms. However, there are no controlled trials concerning the use of steroids in CRPS [13].

Ligands of $\alpha 2\delta$ subunit of the calcium channel, i.e. pregabalin and gabapentin, may be given, especially if the pain is paroxysmal in nature. Treatment should be discontinued if there is no effect after 8 weeks. The therapeutic effect after administration of pregabalin occurs earlier than after gabapentin. Tricyclic antidepressants, such as amitriptyline, may be effective in CRPS despite the lack of randomized studies, especially if a patient has continuously persisting symptoms. Ketamine at sub-anesthetic doses administered intravenously in an inpatient may be an alternative treatment for patients who are treatment-resistant or suffer from exacerbation [102]. Sodium channel blockers (lidocaine and mexiletine) reduced pain intensity in small groups of patients (intravenous infusion of lidocaine), or in individual cases only (mexiletine). Mexiletine is not currently available in Poland due to serious side effects. Topical capsaicin is not recommended in CRPS [86].

Other medications may be used in particular situations. Antispastic drugs (baclofen, diazepam or clonazepam) may be effective in patients with spasticity or dystonia. Intrathecal baclofen should be considered only in the case of spasticity resistant to other forms of treatment [13]. Medicines regulating calcium levels, such as calcitonin and bisphosphonates, may or even should be used if there is a confirmed increase of bone metabolism [73]. In this indication, slow intravenous infusion of pamidronate (60 mg/day within 4 h used for 3 subsequent days) or neridronate (100 mg within 2 h given 4 times for 10 days) has shown some beneficial effects. Dimethyl sulfoxide in the form of a 50% cream can be used if CRPS lasts longer than a year. Another free radical scavenger, N-acetylcysteine at a dose of 600 mg three times daily, may be used for three months in patients with decreased skin temperature [13,72,86]. There are also some single reports on the efficacy of calcium antagonists (nifedipine and nitrendipine), which can be used at appropriate doses for a week, and then only in patients whose response to the therapy is positive [13,72].

If there is evidence that pain is supported by the sympathetic nervous system, e.g. reduction in pain and improvement of blood supply to the limb after sympathetic nerve blocks with a local anesthetic, sympathetic ganglion

neurolysis in the area of CRPS symptom occurrence should be considered instead of the previously used surgical sympathectomy [7,22]. Spinal cord stimulation in selected cases is cost-effective as an adjuvant to the standard pharmacological therapy, but some complications that required additional procedures can be expected in up to 25% of patients [65].

2.3. Recommendations

1. CRPS should be diagnosed according to the diagnostic criteria by a physician experienced in diagnosing pain syndromes.
2. Data from previous trials evaluating the efficacy of various medicines do not allow formulating clear recommendations on a sequence of their use.
3. If opioids and other medicines recommended in neuropathic pain fail or in some particular cases and in specific indications, one may reach for other interventions, such as antispastic drugs or bisphosphonates, and even invasive therapies, such as sympathetic blocks.
4. In the opinion of experts, any treatment is more effective if it is multidirectional, and if it is initiated early.
5. The most important element of multidirectional treatment is active physical therapy, which should not be perceived by a patient as painful.
6. Psychological therapy may be effective if psychological factors are involved in the mechanism of pain, or if a patient hopes for it.

3. Painful diabetic polyneuropathy

3.1. Diagnosis

Both type 1 (insulin deficiency) and type 2 (resistance to insulin) diabetes mellitus are the most common causes of peripheral polyneuropathy in adults. At the moment of type 2 diabetes diagnosis, 8% of patients already present with signs of neuropathy [84]. Diabetes-induced damage to the nerves can affect each type of nerve fibers (sensory, motor and autonomic), both thick myelinated and thin unmyelinated fibers. Apart from damage to the axon (axonal neuropathy), damage to the myelin (demyelinating neuropathy) is found as well. The nerve fibers that are damaged the most often are those in peripheral nerves, plexuses (plexopathy) and radices (diabetic polyradiculoneuropathy), and less commonly in cranial nerves, e.g. oculomotor nerves. Because of the complexity of possible damage, clinical picture of diabetic neuropathy can be divergent (mononeuropathies, multiple mononeuropathies, or polyneuropathies).

Diabetic neuropathy-associated pain can be nociceptive (when the tissues are damaged) or neuropathic (when there is damage to the nervous system). Both types of pain coexist in many cases. Development of diabetic neuropathy and associated neuropathic pain depends on several different mechanisms [116].

Chronic distal symmetric sensorimotor polyneuropathy, which presents with pain in approximately 20–30% of patients, is the most common type of painful diabetic neuropathy. Acute painful sensory polyneuropathy and asymmetric polyradiculoneuropathy occur significantly less often. Painful

compression neuropathies, e.g. carpal tunnel syndrome, are more common among diabetics than in general population.

The clinical picture of diabetic polyneuropathy does not differ from polyneuropathies associated with other diseases. The process of diabetic polyneuropathy is individual and difficult to predict. Polyneuropathy can develop unnoticeably to patients, and even doctors, for many months or even years. Typically, it starts with mild and gradually progressing superficial and deep sensation disturbances, which are later joined by pain, distal muscle weakness, diminished or absent deep tendon reflexes, muscle atrophy and trophic skin lesions. Signs are usually symmetric; initially, they affect feet and then gradually move in the proximal direction. At the same time or slightly later, the same signs are observed in the upper limbs. Signs and symptoms resulting from damage to thick nerve fibers include impaired position and vibration sense, slower nerve conduction and the decreased deep tendon reflexes. Damage to thin fibers leads to pain and impaired temperature perception. Some patients experience dysesthesia, which is defined as unpleasant and painful sensation of tingling, numbness or any other sensation occurring spontaneously or induced by different stimuli and typical for neuropathic pain.

The diagnosis of diabetic neuropathy can be made on the basis of patient's medical history and results of neurological examination, after excluding other possible causes of neuropathy. In the case of damage to thick nerve fibers, a diagnosis can be confirmed by neurophysiological examination. It is recommended to measure the conduction velocity in sensory and motor nerve fibers and determine the response amplitude and terminal latency [31,36]. In order to diagnose thin nerve fiber neuropathy, special examination techniques must be employed, e.g. skin biopsy or quantitative sudomotor axon reflex test [85].

3.2. Treatment

Diabetic neuropathy treatment, especially in advanced cases, is difficult and often ineffective. Complete elimination of pain or the reduction in its intensity by half is achieved only in half of the patients. That is why the following prophylactic measures play a special role: diagnosis of diabetes and its metabolic control, adherence to a proper diet, treatment with insulin or oral medicines in order to keep a glucose level within normal limits on a permanent basis and proper lifestyle. Strict glycaemic control, taking aldose reductase inhibitors or immunoglobulins slow down the disease progression [104]. Infections, exposure to toxic substances and limb injuries should be avoided. Smoking and alcohol use are discouraged as well.

In recent years, a number of recommendations regarding treatment of painful diabetic polyneuropathy have been published by *American Diabetes Association* [17], EFNS [5], American Academy of Neurology (AAN) [19] and multispecialty group of European and American experts (*The Toronto Consensus Panel on Diabetic Neuropathy*) [103], among others. All these publications recommend TCAs, calcium channel α-2-δligands and serotonin-norepinephrine reuptake inhibitors (SNRIs) as a first-line treatment. The next choices are tramadol, alone or together with acetaminophen, or strong opioids. Treatment

should initially start with one medicine, chosen individually from one of the three above-mentioned therapeutic groups on the basis of coexisting diseases and contraindications. If the treatment is unsuccessful or adverse effects make it necessary to discontinue the treatment, it is recommended to switch to another first-line medicine. If a first-line treatment fails, it is recommended to start a combination treatment consisting of medicines from different therapeutic groups, both first-line and next-line choice. AAN and Toronto panel experts clearly point out pregabalin and duloxetine as medicines having the best-documented efficacy in their therapeutic groups.

TCAs, particularly amitriptyline, have had a well-established role among medicines recommended in the treatment of painful diabetic neuropathy for many years. Because of good therapeutic indices in neuropathic pain treatment (number needed to treat [NNT]: 2.1; 95% CI: 1.8–3.9), efficacy similar to other medicines, e.g. duloxetine [63] and pregabalin [8], and low price, many experts consider TCAs as a first-line treatment in diabetic neuropathy. Due to possible severe adverse effects associated with this treatment, the administration of amitriptyline has some limitations. The treatment starts with a dose of 10–25 mg, which is gradually increased up to 50–150 mg/day. Serum level of amitriptyline does not correlate with its analgesic action. Beneficial effects of amitriptyline in neuropathic pain are revealed very quickly, as soon as after the first week of treatment. Lack of efficacy and switch to a new medicine should not be considered before three to four weeks of taking a constant dose of the medicine.

Evidence on the efficacy of first-generation anticonvulsants (carbamazepine and phenytoin) comes from studies performed many years ago; their methodology does not meet current requirements. However, many Polish experts believe that these drugs serve well in practice and recommend their use; this applies especially to carbamazepine [29,32].

Evidence on the efficacy of calcium channel α-2-δ ligands, gabapentin and pregabalin derives from many randomized clinical trials [47,85,92,94]. NNT for gabapentin at a dose of 900–3600 mg/day is 6.4 (95% CI: 4.3–12), while for pregabalin at a dose of 300–600 mg/day it amounts to 4.7 (95% CI: 4.0–5.6) [85].

Standard simple analgesics and NSAIDS, due to lack of clear efficacy in the treatment of neuropathic pain, are not recommended. Tramadol administered orally at a dose of 200 mg/day has clear evidence of efficacy in diabetic neuropathy pain. Strong opioids are particularly recommended in patients with significant pain intensity and resistance to previously taken medicines.

Lidocaine administered intravenously at a dose of 3–5 mg/kg of body weight for 30 min is another medicine that has been used for many years in the treatment of painful diabetic neuropathy. Its analgesic effect is quite short-lasting, which is why it should be administered several times per day. NNT for lidocaine in this indication is 2.5 [85]. Significantly worse effects were observed with mexiletine (NNT: 10), which is currently not recommended due to its adverse effects.

Despite not being approved, 8% capsaicin and 5% lidocaine patches can also be used in some cases. NNT for capsaicin in the treatment of diabetic neuropathy is within the range of 2.5–4.9, while for lidocaine within 2.2–5.9. Open-label pilot study showed that a three-week long treatment with 5% lidocaine patch significantly reduced pain and improved the quality of life [9].

Acupuncture can have a certain significance as an adjuvant treatment. Treatment consisting of six cycles of traditional Chinese acupuncture, administered during a period of 10 weeks, brought considerable pain relief in 77% of patients [2].

3.3.   Recommendations

1. Patients diagnosed with diabetes should maintain an appropriate blood glucose level as a prophylactic measure.
2. First-line treatment of painful diabetic neuropathy includes: TCAs, pregabalin and gabapentin, as well as duloxetine and venlafaxine ER.
3. Second-line medicines in the treatment of painful diabetic neuropathy are: tramadol and strong opioids.
4. Treatment should be commenced with one medicine chosen with regard to individual contraindications and coexisting diseases. If the first-line monotherapy is ineffective or if adverse effects occurred, it is recommended to switch to alternative medication from a different therapeutic group.
5. In case of lack of efficacy, it is recommended to switch to a medicine with a different mechanism of action; change to a second-line medicine (ideally one with a different mechanism of action); or add another first- or second-line medicine (observing the principles of rational pharmacotherapy).

4.   Trigeminal neuralgia

4.1.   Diagnosis

Trigeminal neuralgia (TN) (*neuralgia trigemini, tic douloureux*) is the most common type of face neuralgia. Its prevalence is about 3–6 cases per 100,000 people and increases with age [69]. The pain is most commonly located in the area of the second and third branch of the trigeminal nerve, less often it affects all three branches and in very rare cases it is limited to the first branch only [114]. A characteristic feature of TN is the existence of trigger zones or trigger points, i.e. points or areas which induce paroxysmal pain even with a gentle touch. Most commonly, a few or a dozen of paroxysmal pain attacks can occur within 24 h, yet their frequency can increase with time, thus causing the patient to experience constant pain. Typically, the disease has a relapsing-remitting course, with relapses lasting from a few weeks to several months or even years. Remissions can last for months or even years. However, the periods of remission gradually become shorter, whereas pain attacks increase their intensity and length up to a few hours per day. The character of pain can also evolve from sharp to dull and deep. Pain is usually located on one side, but may affect the other side with another relapse [89]. In-between the attacks, there are no neurological signs or symptoms within the previously painful region.

4.2.   Treatment

Clinical guidelines on NT management were published in 2008 by the joint team of AAN and EFNS experts [27,50]. According to these recommendations, the first-line drugs for NT are

carbamazepine and oxcarbazepine. In case of inefficacy of those drugs, the surgery is indicated. However, grade A recommendation is only for carbamazepine. The studies on oxcarbazepine support recommendation at grade B. Carbamazepine should be administered in gradually increasing divided doses, ranging from 100 to 1200 mg/day. In Poland, oxcarbazepine is not registered as a treatment for TN. Other drugs, like lamotrigine, clonazepam or baclofen (grade C recommendation) can be considered as options for patients who have not responded to carbamazepine.

The efficacy of classic analgesics such as most commonly used NSAIDs is relatively low, similarly to TCAs, which can be used for treating concomitant depression. In case of poor response to pharmacotherapy, botulin toxin therapy can be considered before surgery [28].

The most commonly used invasive methods of TN therapy include Gasserian ganglion thermolesion or surgical procedures: microvascular decompression of the nerve root or stereotactic radiosurgical procedures [68].

4.3. Recommendations

1. Diagnosis of TN can be made based on the occurrence of paroxysmal pain located solely in the region of the trigeminal nerve innervation.
2. Carbamazepine is a first-line treatment for TN.
3. In case of carbamazepine intolerance or known contra-indications for its use, other antiepileptic drugs can be administered (lamotrigine, gabapentin, and pregabalin), as well as baclofen and clonazepam.
4. Interventional procedures should be considered in case of ineffective pharmacotherapy.
5. The therapy with botulin toxin can be considered before surgery.

5. Post-amputation pain

5.1. Diagnosis

Phantom pain experienced in an amputated extremity and stump pain located around the post-surgical scar on the stump, are two out of three basic pain disorders following amputation, apart from non-painful sensation localized in the phantom extremity or illusions that the missing limb is still present [57]. Frequency of the phantom pain following an amputation of an extremity varies and ranges from 4 up to 88%. It depends e.g. on the pain intensity level assumed as the limit to diagnose the case as phantom pain and the time which has passed since the procedure.

5.2. Treatment

Treatment of post-amputation pain comprises not only pharmacotherapy but also psychotherapy, non-invasive electrostimulation, other physical methods, as well as invasive procedures.

The efficacy of many drugs recommended for the management of neuropathic pain is controversial in the case of post-amputation pain. As an example, amitriptyline (up to 125 mg/day) was ineffective in the treatment of post-amputation pain in a study by Robinson et al. [93], whereas other study published one year later did prove the efficacy of amitriptyline at dose of 75 mg/day [110]. Similarly, gabapentin reduced the intensity of phantom pain when administered at a dose of 2400 mg/day in the study of Bone et al. [15], while according to Smith et al. [98], it was not effective at a dose of 3600 mg/day.

Morphine was effective in some studies in decreasing the level of phantom limb pain and stump pain (NNT: 2–4.5), but the analgesic effect proved only a 30% reduction of pain [58,112].

Other drugs used for alleviating the pain caused by amputation include: ketamine administered intravenously, which decreases phantom pain and hyperalgesia [79], dextromethorphan, which decreased phantom pain by 50% in 50% of patients [1], lidocaine which alleviated the stump pain but not phantom pain at a dose of 4 mg/kg administered in an intravenous infusion [113], and calcitonin, which decreased the intensity of the phantom pain when administered intravenously in an early post-operational phase [42].

Cochrane library analysis published in 2011 focused on six therapeutic groups (NMDA antagonists, antidepressants, antiepileptic drugs, anesthetics, opioids and calcitonin) showed only modest efficacy of morphine, gabapentine and ketamine. Memantine and amitriptyline were ineffective in this analysis [3].

Low effectiveness of pharmacotherapy results in other treatment methods being applied, especially physiotherapy and psychotherapy. The outcomes of research assessing the effectiveness of electrostimulation and acupuncture are ambiguous. Massage and passive movements may prevent trophic and vascular changes around the stump. Despite the lack of evidence for its effectiveness, another psychotherapeutic method commonly used in phantom pain is hypnosis. Furthermore, certain studies prove a decrease in phantom limb pain following special visual training (mirror box therapy) [67,80].

Block of a peripheral nervous system and neurodestruction can also be useful in patients with stump pain. If the source of pain is a neuroma, thermolesion can be performed, following a positive outcome of a diagnostic and prognostic nerve block [67,80]. In selected cases of phantom limb pain, thermolesion of the spinal cord or neurostimulation within peripheral nerves, spinal cord or deep brain stimulation can prove effective [78].

5.3. Recommendations

1. Despite the lack of clear evidence for the efficacy of pharmacotherapy in stump pain and phantom limb pain treatment, the following medications are recommended: amitriptyline, gabapentin, pregabalin, tramadol, strong opioids, calcitonin and lidocaine infusions.
2. In stump pain, also physical therapy, peripheral nerve block and neurodestruction can be applied, whereas for phantom pain methods such as thermolesion of the spinal cord, peripheral nerve and spinal cord stimulation as well as deep brain stimulation are available.

3. The efficacy of options commonly used in the treatment of post-amputation pain, such as acupuncture, hypnosis or neuromodulation (TENS), has not been confirmed in clinical trials in a way which would allow their recommendation.

6. Persistent post-operative and post-traumatic pain

6.1. Diagnosis

Persistent post-operative pain (PPP) or persistent post-traumatic pain (PTP) is defined as chronic, pathological pain, which is associated with surgery or trauma and is present for more than normal tissue healing time, and its intensity, character and localization cannot be explained by the occurrence of other pathologies, such as disease recurrence, infection or cancer recurrence. PPP is most often the result of intraoperative or post-traumatic damage to the structures of the peripheral nervous system and that is why it usually has the character of neuropathic pain. Persistent post-operative pain develops most often after surgical procedures within the trunk (20–50% after breast surgery, 30–50% after thoracotomy) or extremities (up to 70% after extremity amputation) [87].

The frequency of the persistent post-operative pain occurrence is highly dependent on the extent and invasiveness of the employed surgical procedure. Application of minimally invasive and nerve-sparing techniques significantly decreases the risk of generation of persistent post-operative pain [64]. Important risk factors for persistent post-operative pain development are also insufficiently treated acute post-operative pain of high intensity, young age, long-lasting surgical procedure and genetic predisposition.

6.2. Treatment

There is evidence that a proper analgesic procedure, when analgesics are administered at an early stage of surgery, can significantly reduce the frequency of persistent post-operative pain. It has been documented inter alia that:

- Epidural analgesia administered before thoracotomy and continued during the intraoperative and post-operative period significantly reduces the frequency of persistent post-operative pain (recommendation class II) [95].
- Continuous epidural analgesia in patients undergoing colon resection procedure decreases the frequency of persistent post-operative pain (recommendation class II) [70].
- Post-surgical wound infiltration with local anesthetic decreases the number of patients with persistent post-operative pain after brain tumor resection (recommendation class II) [10].
- Perispinal nerve block before, during and after the mastectomy procedure reduces the frequency of persistent post-operative pain in such patients (recommendation class II) [62].
- Administration of gabapentin or mexiletine in the perioperative period reduces the frequency of neuropathic pain after the mastectomy procedure (recommendation class II) [46].

- Administration of intravenous lidocaine infusions at a dose of 2–3 mg/kg of body weight for 7–10 days after the surgery in patients from the risk groups reduces the frequency of persistent post-operative pain occurrence and intensity [49].
- If persistent post-operative pain occurs, causative management, e.g. decompression or fusion of the damaged nerve, should be performed whenever it is possible. Other patients should be treated symptomatically. Since in most cases persistent post-operative pain is of neuropathic character, the therapy should be conducted in accordance with the principles of neuropathic pain treatment. In the case of localized pain, it is advisable to administer 5% lidocaine patch in monotherapy or together with systemic medicines. Appropriate pharmacotherapy should be combined with psychotherapy and proper rehabilitation. In the treatment of specific PPP syndromes not responding to pharmacotherapy, interventional methods of pain relief are encompassed [40].

6.3. Recommendations

1. In order to reduce the risk of persistent post-operative pain development, it is advisable to apply:
   a regional anesthesia techniques: infiltration of post-surgical wound with local anesthetic; perispinal nerve block in breast surgery; continuous epidural anesthesia in thoracic and abdominal surgeries;
   b gabapentin or pregabalin during the perioperative period.
2. Although there is no evidence according to EBM criteria (poorly reliable data), it is advisable to use intravenous lidocaine infusions in patients from the risk groups.
3. Although there is no evidence according to EBM criteria (poorly reliable data), persistent post-operative pain should be treated with:
   a Implementation of causative procedures, e.g. decompression or fusion of the damaged nerve, if it is possible.
   b Compliance with neuropathic pain treatment recommendations.
   c In the case of localized pain, administering 5% lidocaine patch in monotherapy or together with systemic medicines.
4. In the treatment of specific PPP syndromes not responding to pharmacotherapy, interventional methods of pain relief should be considered.

7. Neuropathic pain in cancer patients

7.1. Diagnosis

Pain in cancer patients may have different origins. The mechanism of this pain is very often complex, both nociceptive and neuropathic. It is estimated that at least 15–20% of cancer patients experience neuropathic pain at different stages of the disease. In the advanced stage of the disease, this proportion increases up to 1/3 of patients.

Neuropathic pain concurrent with cancer can be a result of:

a. cancer through the compression or infiltration of the central or peripheral [48,60] nervous system or associated with paraneoplastic syndrome [14];
b. anticancer therapy in the form of persistent post-operative pain caused by intraoperative damage to nervous system structures (most often in patients after thoracotomy, mastectomy and amputation [108]) or as neuropathic pain syndromes caused by radiotherapy (nervous tissue necrosis or a lesion of plexuses [34]) and chemotherapy [45];
c. diseases related to a cancer, for example post-herpetic neuralgia; acute varicella zoster virus infection can be observed in 1–2% of patients suffering from a cancer; as a consequence, post-herpetic neuralgia develops in 25–50% of people infected by this virus [37];
d. other diseases not related to cancer, e.g. painful diabetic polyneuropathy.

Neuropathic pain associated with anticancer therapy most often has the form of peripheral polyneuropathy and is observed in 3–7% of patients receiving monotherapy and in up to 38% of patients taking multidrug chemotherapy [59]. Peripheral polyneuropathy develops most often after taking platinum derivatives (cisplatin, carboplatin and oxaliplatin), vinca alkaloids (vincristine), paclitaxel and bortezomib. It should be noted that chemotherapy-induced polyneuropathy (CPIN) is the most common neurological adverse effect of anticancer therapy. Each of the medicines taken in cancer chemotherapy, through different mechanisms, can cause damage to sensory nerves. The development of neuropathy involves gradual increase of symptoms, which are exacerbating along with the duration of chemotherapy. The symptoms of neuropathy have a severe, negative impact on the patients' quality of life. They are one of the most common causes of reducing the dose or replacing a particular chemotherapy agent.

7.2. Treatment

There are no studies which would allow to formulate recommendations on the highest level of evidence (A). In practice, opioids are the first-line treatment of neuropathic pain in cancer patients. This is, among others, due to the fact that neuropathic pain syndromes in this group of patients are the most common cause of pain of considerable intensity (6–10 points in the 11-point numeric scale), which is the indication to take strong opioids. Strong opioids preferred in the neuropathic pain therapy include buprenorphine (because of its anti-hyperalgesic effect), oxycodone (because of the fact that, apart from stimulating μ receptors, it is also the agonist of the κ opioid receptor) and methadone (because it blocks NMDA receptors and affects norepinephrine and serotonin levels). Taking methadone may result in several drug interactions and is associated with variable, unpredictable pharmacokinetics. Because of these reasons, it is most often considered as an opioid taken after unsuccessful therapy with other opioids [21,44]. In the treatment of neuropathic pain of moderate intensity (4–6 points in the 11-point numeric scale) tramadol is recommended [55].

In order to induce more effective analgesia, it is recommended to take an opioid together with gabapentin or pregabalin [23]. It was also proved that pregabalin, as compared to amitriptyline and gabapentin, significantly reduces the demand for morphine in cancer patients [77], guarantees more satisfaction from treatment and causes less adverse events as compared to gabapentin [91].

In the treatment of pain in patients suffering from CPIN, a significant reduction of pain intensity was observed after therapy with duloxetine [99]. Similarly, venlafaxine proved to be effective in the prophylaxis and relief of acute neurotoxic symptoms caused by oxaliplatin – the pain was completely eased in 31.3% of patients [35].

Interventional (neurodestructive) techniques can be applied in selected pain syndromes in cancer patients.

7.3. Recommendations

1. In the case of neuropathic pain of moderate intensity, it is advisable to start the analgesic treatment with tramadol, whereas in the case of severe pain it is recommended to start the therapy with a strong opioid.
2. By adding pregabalin or gabapentin, the therapy can be more effective and the dose of opioids can be reduced.
3. In the treatment of pain associated with post-chemotherapy painful polyneuropathy, it is recommended to take duloxetine or venlafaxine.

8. Painful neuropathies in HIV infection

8.1. Diagnosis

Painful sensory polyneuropathy (PSN) is the most common neurological complication of HIV infection [109]. Two most frequent PSN forms in HIV infection (PSN-HIV) are distal sensory polyneuropathy (DSP) and antiretroviral toxic neuropathy (ATN). DSP is caused by the virus, while ATN is the effect of the treatment of HIV infection. Although the mechanisms of nerves damage are completely different, the clinical picture of DSP and ATN is similar. The most common factors increasing the risk of DSP are: elder age and disease progression indices such as high viral load and low CD4 cells count [25].

8.2. Treatment

Most of the controlled studies assessing the efficacy of different medicines in PSN-HIV have been conducted on small groups (less than 50 patients). Level A evidence has been provided only for 8% capsaicin patch [20]. Single publications described significant alleviation of pain in PSN-HIV after treatment with lamotrigine [96] and gabapentin [52]. Treatment with gabapentin reduced not only the pain (by 44%), but also improved the comfort of sleep (by 49%). Five-percent lidocaine [43], pregabalin [97] as well as amitriptyline [74] did not produce clinically significant pain relief in patients diagnosed with PSN-HIV.

Hypnosis assessed in an uncontrolled study reduced the pain intensity by 44% in patients with PSN-HIV. Pain relief was observed over the period of 7 weeks [33].

Recommendations

1. Eight-percent capsaicin patch is recommended in the treatment of PSN-HIV, together with gabapentin and lamotrigine (despite their low level of evidence).
2. Due to the negative results of previous studies, it is not recommended to take amitriptyline, pregabalin or 5% lidocaine patches.

9.　Central pain

9.1.　Diagnosis

According to the first definition of central pain, published by IASP in 1986, it is "a pain that accompanies a central nervous system lesion" [101]. At present, in the most common opinion of experts, central pain is a central type of neuropathic pain defined as "a pain caused by a direct lesion or disease of the central somatosensory nervous system" [107].

Contemporary epidemiological data show that pain, especially chronic one, is a frequent symptom of primary CNS diseases, and is present in 20–40% of patients; however, in some diseases, e.g. Parkinson disease, the pain is present even in 40–60% of patients [16], but only partially it is a pain of central origin. Because of the predominant contribution of central pain mechanisms to the generation of pain and, first of all, persistence of pain, some researchers believe that a number of common pain syndromes treated so far as peripheral, such as fibromyalgia, irritable bowel syndrome or tension-type headache, should be regarded and treated as central pain syndromes [88]. However, there is no direct evidence that would allow to link these syndromes to a primary dysfunction or lesion of the central nervous system.

The pathomechanism of central pain is complex. A number of mechanisms have been documented: e.g. disorganization of cell-to-cell signaling resulting from nervous system lesions, hypofunction of GABAergic inhibitory system or microglial activation [51,106]. Specific mechanisms are responsible for the occurrence of pain in different nervous system diseases, such as multiple sclerosis (MS), central post-stroke pain or Parkinson disease. These mechanisms are: trigeminal neuralgia and dysesthesias in MS, spino-thalamic tracts dysfunctions in a stroke, and dystonia and hypokinesia in Parkinson disease.

Usually, the onset of central pain occurs after a delay of weeks or months since the first symptoms of the acute phase of the disease have appeared, e.g. stroke or injury, or after several years of chronic disease, e.g. Parkinson disease. Originally, the pain is mild or incontinuous, but it increases gradually over the next weeks and months. The pain is often experienced as sharp, pricking and shooting, and quite often as hot and burning. It is accompanied by painful paresthesias (dysesthesias). Usually, there is no spontaneous remission, the pain is continuous and is often present for life.

The risk of central pain occurrence does not correlate with the area and location of the lesion, however, in some syndromes, such as syringomyelia, the pain is more likely to occur when the spinal lesion is more extensive.

Central post-stroke pain (CPSP) is the better described pain resulting from a lesion in the central nervous system. It is one of many possible chronic post-stroke pains, next to shoulder pain, painful spasticity and tension-type headache. It is estimated that different forms of chronic post-stroke pain are present in 11–55% of patients, while CPSP, according to different statistical data, is present in 1–12% of post-stroke patients [66].

Central pain in Parkinson disease is associated with the involvement of the dopaminergic system in the generation of chronic pain. In Parkinson disease, people complain of pain significantly more frequently than the general population at the same age and more often than in other neurodegenerative diseases, such as Alzheimer disease [11]. Pain in Parkinson disease can have a direct connection with the disease (e.g. higher pain intensity in "off" states than in "on" states, dystonic pain) or can be caused by secondary disorders, for example musculoskeletal pain as a consequence of increased tension and posture disorders, or radicular pain.

There is an evidence that basal ganglia are involved in many aspects of pain processing, both in its sensory-discriminative dimension, and in the emotional-affective and cognitive aspect, as well as in pain modulation processes. This is also confirmed by the studies on functional neuroimaging in humans. Basal ganglia are activated both in acute and chronic pain, and this activity is modulated by the administration of analgesics. Studies performed on human and animal models showed that the threshold of pain in Parkinson disease is decreased and administration of levodopa increases it significantly [18].

Central pain occurs particularly often in post-traumatic spinal cord injury, and is then called spinal cord injury pain. Pain as a result of spinal cord injury is present in 60–70% of patients, and 30% of patients describe its intensity as very high and lasting more than a year. In these cases, pain may be caused by mechanical instability of the spinal cord (resulting in its displacement and compression by bone structures), muscle spasm, but also pressure applied to the nerve root and other pathologies leading to neuropathic pain, such as cauda equina injury, syringomyelia or segmental deafferentation pain. Distinction between spinal cord injury pain and the other abovementioned neuropathic pains based on a clinical picture is not possible, except for pain in a specific location (in the nerve roots or segments of the spinal cord).

Pain in MS, though not so common as in the post-traumatic spinal cord injury or in Parkinson disease, is the cause of suffering and deterioration in the quality of life in a significant number of patients. Different forms of chronic pain in MS are diagnosed in more than 20% of patients, most often in people over the age of 60 and after several years since the onset of the disease [82]. Patients particularly often experience painful burning dysesthesias and other forms of acute pain, such as trigeminal neuralgia and painful muscle spasms. A lot of patients suffer from the combination of different pain syndromes, e.g. dysesthesias, headaches and musculoskeletal pains, particularly in the sacral area. For therapeutic purposes, the pain in patients with MS can be categorized into neuropathic pain directly associated with the disease, pain indirectly associated with the disease, pain resulting from therapy and pain not associated with MS [90].

9.2.   Treatment

Recommendations oriented particularly at central pain (central neuropathic pain) were formulated by a couple of expert groups, e.g. EFNS [5] and IASP Neuropathic Pain Special Interest Group – NeuPSIG [38]. The most recent publications of these groups were issued in 2010 and are very similar to each other. According to EFNS experts, the first-line treatment in the therapy of central pain includes: pregabalin (level A), gabapentin (level B, but A in other neuropathic pains) and amitriptyline (level B, but A in other neuropathic pains). As a second-line treatment, they have chosen tramadol (level B). Strong opioids (level B) were recommended as second-line and third-line treatment only when there is no need for long-term therapy. Lamotrigine can be taken in CPSP or in spinal cord injury pain if the spinal cord damage is incomplete or in the case of allodynia to touch stimuli (level B). Cannabinoids can be taken to relieve pain in patients with MS if other forms of treatment fail (level A). Medications such as valproic acid or mexiletine were regarded as ineffective in central pain treatment [5].

In 2012, a group of experts from South Africa issued their recommendation, in which they proposed pregabalin and amitriptyline as first-line treatment, indicating pregabalin as preferable because of its documented efficacy, small number of contraindications and better efficacy-to-risk ratio. Amitriptyline or other TCAs, taking contraindications into account, can be a first choice treatment in people with depression, anxiety and insomnia. After a 2–4 week assessment period, in case of lack of response or bad tolerance, pregabalin should be changed to amitriptyline, or inversely. Further lack of response is an indication for the next option – tramadol – and then a strong opioid [24]. Few results of randomized clinical trials, which have been published over the last couple of years, do not change the abovementioned recommendations.

9.3.   Recommendations

1. While diagnosing central pain, one needs to prove its direct association with a lesion or disease of the central nervous system. When possible, the etiology of central pain should be indicated, e.g. central post-stroke pain.
2. Pregabalin is the first-line treatment in the therapy of central pain. In people suffering from depression, anxiety and insomnia, taking into account contraindications, amitriptyline or another product from the TCAs group can be a first choice treatment.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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