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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 one

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ABSTRACT

Neuropathic pain still present a major diagnostic and therapeutic challenge despite considerable progress in understanding of its mechanisms and publication of number of studies which assessed the efficacy and safety of drugs used in the symptomatic treatment. In practice, it is diagnosed less frequently than recognised in the epidemiological studies, and many patients do not achieve satisfactory outcomes of treatment. 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 neuropathic pain, with special focus on the published international recommendations, and formulated recommendations on neuropathic pain diagnosis and treatment, in accordance with the principles of evidence-based medicine. The paper presents also background information on the neuropathic pain definition, epidemiology, pathomechanism and method of assessment. The diagnosis of neuropathic pain may be established based on medical history and physical examination

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including special assessment of the somatosensory system. First-line drugs used in pharmacological management of neuropathic pain are: tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, gabapentin, pregabalin, opioids and lidocaine patches.
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1. Introduction

Neuropathic pain is a unique type of pain characterised by specific clinical presentation and low efficacy of analgesics and anti-inflammatory agents. Despite relatively high prevalence, it is rarely diagnosed, and even more rarely adequately and effectively treated. In the last years several evidenced-based recommendations on the diagnosis and management of this type of pain have been published. They include recommendations of expert groups commissioned by international medical associations, such as the International Association for the Study of Pain (IASP) and the European Federation of Neurological Societies (EFNS), as well as recommendations of national research associations in countries such as Australia, France, Canada and South Africa. Some of these recommendations have been presented previously to Polish physicians [1,2]. Differences related to the health care system and drug availability on the Polish pharmaceutical market necessitate adapting the recommendations to Poland-specific conditions.

The review of literature and recommendations was the initiative of physicians and researchers gathered in the Commission of Pain Pathophysiology of the Committee of Neurological Sciences of the Polish Academy of Sciences and followed by formation of the expert group representing the Polish Association for the Study of Pain and the Polish Neurological Society. At successive meetings, the experts reviewed the literature on neuropathic pain, paying special attention to the published review papers and recommendations, as well as results from randomised clinical trials. The review was focused on the diagnosis and management of neuropathic pain and its specific syndromes, and complemented with neuropathic pain definition, epidemiology, pathomechanism and assessment methods. The paper was divided into two parts: part one, which is being presented now, focused on the overview of neuropathic pain assessment and treatment, and part two, which will be published in the next issue of the journal, focused on the most common neuropathic pain syndromes.

The recommendations are addressed primarily to physicians of different specialities, who diagnose and treat chronic pain in their everyday practice. We hope that the publication will be helpful to the physicians and facilitate improvement of the pain management standards in Poland.

2. Definition of neuropathic pain

Neuropathic pain is not a disease, but a syndrome manifested by more or less specific symptoms and signs, caused by a range of different disease and lesions. According to the first definition appeared in the Classification of Chronic Pain published by IASP in 1994 [3], neuropathic pain is the ''pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system''. The definition has been widely used for many years, despite critical comments made by many researchers. The most recent definition proposed by experts and approved by the Task Force on Taxonomy of the IASP is as follows: ''pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'' [4].

Neuropathic pain may arise as a direct consequence of a lesion or disease of the peripheral (peripheral neuropathic pain) or central (central neuropathic pain) somatosensory nervous system [5]. The cause of neuropathic pain may be known, e.g. infection, injury or metabolic disorder, or unknown. The same lesion or disease may cause the development of neuropathic, as well as somatic or even psychogenic pain. Therefore, neuropathic pain may be the only one of the component of a patient's acute or chronic pain syndrome.

Definite diagnosis of neuropathic pain is not always possible. The authors of the new criteria of neuropathic pain defined also the four criteria for grading of certainty of neuropathic pain diagnosis, as follows:

1. Pain with a distinct neuroanatomically plausible distribution.
2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system.
3. The presence of negative or positive neurologic signs concordant with the distribution of pain in neurological examination or in the more objective confirmatory tests (quantitative sensory testing, laboratory tests).
4. Demonstration of the relevant lesion or disease by at least one confirmatory test.

Using these criteria neuropathic pain can be classified as defined (all criteria present), probable (1 and 2, plus either 3 or 4) or possible (1 and 2, without confirmatory evidence from neurological examination and confirmatory tests) [4].

3. Epidemiology of neuropathic pain

Only few epidemiological studies of neuropathic pain have been carried out and published as yet. They are difficult to make because of subjectivity of the sensation of pain, difficulty setting apart neuropathic pain from complex pain syndrome and lack of a widely approved standard tool for identifying neuropathic pain.

The British study on the cohort of general practitioner's patients evidenced neuropathic pain in 8.2% of adult patients having significantly higher pain intensity than others [6]. The French study in a randomly selected adult population using the *Douleur Neuropathique 4 Questions* (DN4) questionnaire, identified neuropathic pain in 6.9% of 23,712 examined persons [7]. The most common risk factors for neuropathic pain included: female sex, elderly age, lower level of education and living in a rural area. Neuropathic pain was associated with worse health, i.e. compromised physical, mental and social well-being [7–11].

4. Pathomechanism of neuropathic pain

Neuropathic pain is a result of many processes related to inefficient repair capabilities and adaptation to a lesion or disease of the nervous system. Neuronal overexcitability, which characterises all neuropathic pains, is not a manifestation of one mechanism but rather results from a combination of many factors which, having accumulated, determine the degree and type of overexcitability in individual patients and in individual pain syndromes.

The best known pathomechanisms responsible for the development of neuropathic pain can be divided into at least three groups. The first one includes changes in electrophysiological properties of the cellular membrane of the first sensory neuron, which include both changes in nociceptor excitability (lowered excitability threshold, possibility of spontaneous excitations) and changes in the release of neurotransmitters. The group also includes changes in gene expression in neuronal cell body. The second group of potential mechanisms underlying neuropathic pain is related to changes in impulse processing in the dorsal horns of the spinal cord. Many researchers emphasise the special role of intensification of glutamatergic transmission, dysfunction of the descending inhibitory systems in the spinal cord, microglial activation and changes in neuronal morphology consisting in, among others, rearrangement of synaptic junctions. The third group includes disorders in higher levels of the central nervous system, such as disturbed balance between the activity of ascending excitatory systems and descending inhibitory (antinociceptive) systems. Furthermore, the autonomic nervous system dysfunction may be also involved in the development of neuropathic pain [12,13].

5. Clinical assessment of a patient with neuropathic pain

Examination of a patient with neuropathic pain begins with taking detailed medical history including the duration and characteristics of pain (its intensity, changes over time, sensation types, etc.), its relation on other factors, accompanying symptoms and response to treatment.

Medical history should reveal whether or not pain characteristics and location are consistent with diagnostic criteria for neuropathic pain and the relevant lesion or disease of the nervous system might be a probable cause of pain.

The second step is physical examination, both general and neurological, focused in particular on somatosensory system assessment. The examination should include the sensation of touch, pain (pinprick), temperature (warmth and cold) and vibration, as well as temporal summation. The area where the complaints are most intense should be examined and compared with the opposite side. The aim of the examination is to identify negative (loss of function) and positive symptoms (e.g. hyperalgesia, allodynia) related to one or several types of sensation most likely to have resulted from a lesion or disease of the somatosensory nervous system.

Further diagnostic evaluation may be performed to document the presence of a specific disease of the nervous system (e.g. brain imaging documenting past stroke in patients with central pain) or a lesion of the sensory pathways in the pain area (e.g. skin biopsy documenting loss of small fibres in the case of neuropathy) [14].

6. Quantitative sensory testing and laboratory assessment

Quantitative sensory testing (QST) using appropriate, usually relatively simple tools, is a method complementing the neurological examination. Measuring the threshold of sensory perceptions in response to external stimuli of controlled intensity, both increasing and decreasing, it allows comparative assessment of positive sensory symptoms, such as mechanical and thermal allodynia and/or hyperalgesia. The assessment of the sensory perception over time may predict and monitor treatment outcomes.

Pain assessment may also involve laboratory tests, such as nerve conduction study (NCS), somatosensory-evoked potential (SEP), laser-evoked potential (LEP) or intraepidermal nerve fibres (IENF) density quantification in a skin biopsy specimen. However, these techniques require an appropriate equipment and experience of the examiners; they are performed in only few clinical research centres.

Clinical (neurological), quantitative and laboratory methods employed for the assessment of specific sensation types, in relation to the types of nerve fibres involved in nociception, are presented in Table 1 [4,14].

7. Neuropathic pain screening scales

The screening scales have been developed for epidemiological studies and can be of use in identifying neuropathic pain or the presence of a clear neuropathic component in the patient's pain syndrome. They may be used if medical history or physical examination reveal typical signs of neuropathic pain. Each scale has its own sensitivity and specificity. The most widely used screening scales include:

- *Leeds Assessment of Neuropathic Symptoms and Signs* (LANSS). The scale comprises 5 questions about pain and 2 items related to clinical examination. The scale specificity is 85% and sensitivity 80%. The score of 12/24 means pain of predominantly neuropathic origin [14–16]. The scale has been validated in a number of centres [14].

Table 1 – Clinical, quantitative and laboratory sensory testing methods [4,14].

Fibre type	Sensation type	Testing method		
		Clinical	QST	Laboratory tests
Aβ	Touch	Cotton wool ball	von Frey filaments	NCS, SEP
	Vibration	Tuning fork	Vibrameter	NCS, SEP
Aδ	Pain – pin prick	Stick	Weighted needles	NCS, LEP, IENF density quantification in the skin biopsy
	Cold	Thermoroller	Thermotest or other tool for assessing reaction to changing temperature	No tool
C	Warmth	Thermoroller	Thermotest or other tool for assessing reaction to changing temperature	NCS, LEP, IENF density quantification in the skin biopsy
	Pain – burning	No tool	Thermotest or other tool for assessing reaction to changing temperature	NCS, LEP, IENF density quantification in the skin biopsy

- *Douleur Neuropathique 4 Questions* (DN4). The scale comprises 7 questions about symptoms and 3 items related to clinical examination. The scale specificity is 83% and sensitivity 90%. The score > 4/10 means pain of predominantly neuropathic origin [14,17]. The scale has been validated in a number of countries.
- *Pain* DETECT. The scale comprises 9 weighted questions about symptoms. It does not include items related to clinical examination. The scale specificity is 85% and sensitivity 80%. The score > 19/38 means pain of predominantly neuropathic origin [18].
- *Neuropathic pain questionnaire* (NPQ) comprises 12 questions, 10 of which are related to symptoms or sensory response, and 2 are related to an emotional aspect. A short form of NPQ comprises 3 questions about response to touch. The scale specificity is 66% and sensitivity 74% [19].

8. Diagnosis of neuropathic pain – recommendations

1. The diagnosis of neuropathic pain can be established by a physician based on characteristic clinical presentation and relation to a lesion or disease of the nervous system; in the case of lack of experience in diagnosing neuropathic pain, confirmation by a relevant specialist or in a reference centre is recommended.
2. The diagnosis of the neuropathic pain should be accompanied by the level of its certainty.
3. If an aetiological factor is known, it should be included in the diagnosis, e.g. diabetic neuropathic pain, post-herpetic neuropathic pain, central post-stroke pain, or neuropathic pain following spinal cord injury.
4. The screening tests are a useful diagnostic method, but their results cannot be the only basis for the diagnosis of neuropathic pain.
5. Pain assessment with laboratory tests is recommended in dubious cases and only in centres that have relevant experience.

9. Management of neuropathic pain – review of published recommendations

The first evidence-based recommendations for pharmacological management of neuropathic pain in the form of algorithm, were published by IASP experts in 2005 [20]. They analysed 105 controlled studies and assessed the treatment efficacy using measures such as NNT (number needed to treat – the number of patients that need to be treated for one to benefit, e.g. at least 50% relief in pain, compared with a control in a clinical trial) and NNH (number needed to harm – the number of patients need to be exposed to a risk-factor over a specific period to cause harm in one patient that would not otherwise have been harmed). In their opinion, the efficacy of tricyclic antidepressants (TCAs) and two anticonvulsants (gabapentin and pregabalin) in neuropathic pain are supported by the greatest number of studies. The best measure of NNT in peripheral neuropathic pain, was found for TCAs, followed by opioids and gabapentin and pregabalin.

The second version of the same IASP experts' recommendations appeared in 2007 in the form of guidelines [21]. The authors proposed a four-step approach to the management of neuropathic pain and specified drugs to be used as first-line, second-line and third-line of treatment.

The guidelines of a group of European experts from EFNS appeared in 2006. There were related not only to the drugs' efficacy but also to data on the quality of life, the drugs' effect on sleep and the impact of comorbidities [22]. The guidelines concerned the most common neuropathic pain syndromes, i.e. painful peripheral polyneuropathy (including diabetic polyneuropathy), post-herpetic neuralgia, trigeminal neuralgia and central pain. The revised versions of the guidelines appeared in 2010 [23–25].

In subsequent years, other recommendations were also published by experts, e.g. from the French Society for the Study and Treatment of Pain [26], Canadian Pain Society (2007) [27], Australian Pain Society [28] and expert panel from South Africa [29].

A slightly modified four-step approach to the management of neuropathic pain as proposed by IASP experts in 2007 is presented in Table 2.

Based on the level of evidence from randomised trials, the following drugs are recommended by IASP experts for the first-line treatment of neuropathic pain [21]: TCAs (first nortriptyline and desipramine, which are unavailable in Poland, and subsequently other TCAs: amitriptyline, imipramine, etc.), serotonin and norepinephrine reuptake inhibitors (SNRIs; venlafaxine and duloxetine), calcium channel α2-δ ligands (gabapentin and pregabalin) and topical 5% lidocaine patches. Opioids (morphine, oxycodone, methadone, levorfanol [*levorfanol is unavailable in Poland; authors' note*]) and tramadol are recommended for the second-line treatment, although in some clinical situations they may be used in the first-line treatment. Other drugs, which are recommended for the third-line treatment, include other anticonvulsants (carbamazepine, valproic acid, lamotrigine, oxcarbazepine, topiramate), other antidepressants (bupropion, citalopram, paroxetine), mexiletine, dextromethorphan and topical capsaicin.

Based on a similar review of literature in accordance with the principles of evidenced based medicine (EBM), EFNS experts developed recommendations for pharmacotherapy of specific neuropathic pain syndromes. In painful diabetic peripheral neuropathy they recommended gabapentin, pregabalin, TCAs, duloxetine and venlafaxine for the first-line treatment, and opioids and tramadol for the second-line treatment. In post-herpetic neuropathy, gabapentin, pregabalin, TCAs and 5% lidocaine patches were recommended for the first-line treatment, while capsaicin and opioids for the second-line treatment. In trigeminal neuralgia, carbamazepine and oxcarbazepine are recommended for the first-line treatment, and surgery for the second-line treatment [30].

Neuropathic pain is often refractory to pharmacological treatment, which is why other modalities, including interventional ones, are used. In 2013, Dworkin et al. presented recommendations for interventional modalities for the management of neuropathic pain [30]. The authors assessed published systematic reviews, clinical trials and existing guidelines on the use of interventional modalities in the management of neuropathic pain. In none of the most common pain syndromes (herpes zoster and post-herpetic neuralgia, painful diabetic neuropathy and other peripheral neuropathies, pain following spinal cord injury, post-stroke pain, radiculopathy and failed back surgery syndrome [FBSS], complex regional pain syndrome [CRPS], neuralgia and trigeminal neuropathy) have strong recommendations for interventional modalities been developed. Weak recommendations in terms of efficacy and safety are as follows: epidural steroids for herpes zoster and radiculopathy and spinal cord stimulation in patients with FBSS and CRPS type 1. Of the interventional modalities used in patients with trigeminal neuralgia, microsurgical decompression produced best and most durable outcomes. However, the effectiveness of interventional modalities in the management of neuropathic pain management is limited – partial relief is achieved in not more than 40–60% of patients. The authors emphasise the fact that in future the use of interventional modalities should undergo scrutiny which should include documented randomised trials, long-term follow-up and comparative ''head-to-head'' trials.

Table 2 – Stepwise management of neuropathic pain [21].

Step 1
- Assess pain and establish the diagnosis of neuropathic pain (if uncertain about the diagnosis, refer to a specialist)
- Establish the cause of neuropathic pain
- Identify comorbidities (e.g. cardiac, renal or hepatic disease, depression, gait instability) that might be relieved or exacerbated by neuropathic pain treatment
- Educate the patient (about the diagnosis, available treatment and realistic expectations)

Step 2
- Initiate therapy of the disease causing neuropathic pain, if applicable
- Initiate symptomatic treatment with the following (first-line) drugs:
  - TCA or SNRI (duloxetine, venlafaxine)
  - calcium channel α2-δ ligand, either gabapentin or pregabalin
  - topical lidocaine used alone or in combination with other first-line drugs in patients with localised peripheral neuropathic pain
  - Opioid analgesics or tramadol alone or in combination with other first-line drugs in patients with acute neuropathic pain, neuropathic cancer pain or episodic exacerbation of severe pain
- Evaluate patient for psychotherapy

Step 3
- Reassess pain and quality of life frequently
- If substantial pain relief (e.g. pain reduction to ≤3/10) and no clinically significant adverse effects, continue treatment
- If partial pain relief (e.g. pain remains ≥4/10) after an adequate dose for adequate time, add a second first-line drug
- If inadequate pain relief (e.g. <30% pain reduction) after an adequate dose for adequate time, switch to an alternative first-line drug

Step 4
- If treatment with first-line drugs is ineffective, consider second- and third-line drugs or referral to a reference centre

10. Pharmacologic management of neuropathic pain

Drugs from the following drug classes have been proven effective in the management of neuropathic pain:

- antidepressants,
- anticonvulsants,
- opioid analgesics and tramadol,
- topical drugs (lidocaine, capsaicin),
- NMDA receptor antagonists.

It should be emphasised that the documented effectiveness applies to specific drugs and doses. Based on the published data on the strength of evidence for their effectiveness, the drugs are classed as first-, second- and third-line drugs for the treatment of neuropathic pain (IASP recommendation) or for the treatment of specific neuropathic pain syndromes (EFNS recommendations). First-line drugs available on the Polish pharmaceutical market include:

- TCAs (amitriptyline, imipramine),
- SNRI (duloxetine, venlafaxine),
- calcium channel α2δ ligands (pregabalin, gabapentin),
- lidocaine patch 5% – for localised peripheral neuropathic pain,
- carbamazepine and oxcarbazepine – for trigeminal neuralgia only.

Treatment should be started with a first-line drug, and the dose should be gradually titrated upwards until a satisfactory effect has been achieved. If the effectiveness is unsatisfactory or adverse effects occur, another first-line drug may be used or added to the previously used drug from another drug class. If the effect is still unsatisfactory, second-line or third-line drugs can be used, alone or in combination, tailored to the individual patient's needs. In the case of defined contraindications or co-existing diseases or symptoms, as well as the need for other therapies, the treatment of neuropathic pain should also be individually tailored [31].

The effectiveness of drugs used for the treatment of neuropathic pain is often dose-dependent. The recommended initial doses, their titration upwards, maximum doses and precautions for use of first-line drugs are presented in Table 3.

11. Antidepressants

Antidepressants are indicated for the treatment of neuropathic pain, as well as, pain coexistent with depression (level 1 according to EBM) [23]. Due to the inhibitory effect on serotonin and norepinephrine reuptake, they increase the activity of the descending antinociceptive system and have a synergistic effect with opioid analgesics. In addition to the potentialisation of the analgesic effect of opioids, they also have myorelaxant and anxiolytic effects, particularly serotonin reuptake inhibitors. Inhibition of serotonin and norepinephrine reuptake from the synaptic cleft, in addition to having inhibitory effect on nociception processes in the spinal cord, also has an inhibitory effect on sodium channels and the processes of NMDA receptors activation.

In the management of neuropathic pain, effectiveness has been documented in the case of TCAs (amitriptyline, desipramine, imipramine, nortriptyline) and SNRIs (duloxetine, venlafaxine). Other frequently used antidepressants, such as SSRIs or mianserine, do not have such an effect; research results are either controversial or negative. Nevertheless, they may be used in specific pain syndromes, e.g. drugs from the SSRI class in the treatment of some central neuropathic pain syndromes. Mianserine and mirtazapine may be used as adjuvants for potentialisation of opioid analgesia.

TCAs are not sufficiently effective in the management of HIV-associated neuropathy, chemotherapy-induced peripheral neuropathy or radiculopathy after failed back surgery [5,24,25]. Amitriptyline should be used with caution in elderly patients with a cardiovascular disease or narrow angle glaucoma and in men with prostate gland hypertrophy. What may also be a problem is the TCA-induced sedation and high

Table 3 – Recommended doses, precautions for use and most important contraindications for first-line drugs for the treatment of neuropathic pain.

Drug	Initial dose	Dose titration	Maximum daily dose	Precautions or contraindications
Amitriptyline	25 mg at bedtime	25 mg, every 3–7 days	150 mg	Substantial anticholinergic effects
Duloxetine	30 mg	30 mg, every week	120 mg	Not to be used in patients with glaucoma
Venlafaxine	37.5 mg once or twice daily	75 mg, every week	225 mg	Dose adjustment in patients with renal failure is necessary
Pregabalin	75 mg twice daily	300 mg over 3–7 days	600 mg in two divided doses	Caution should be exercised when used in patients with renal failure
Gabapentin	100–300 mg at bedtime or 100–300 mg three times daily	100–300 mg every 1–7 days	3600 mg in three divided doses	Dose should be reduced in patients with impaired renal function
Lidocaine patch 5%	Maximum 3 TTSs for up to 12 h/day	Usually, no dose up-titration is required	Maximum 3 TTSs for 12–18 h/day	Local hypersensitivity reactions are possible
Tramadol	50 mg once or twice daily	50–100 mg every 3–7 days	400 mg/day in divided doses; 300 mg/day in patients aged over 75 years	Caution should be exercised when used in patients with renal failure
Strong opioids (morphine, oxycodone, methadone)	10–15 mg of morphine every 4 h or other opioids in equivalent doses	Once the therapeutic dose has been set, converting a controlled-release oral form is recommended	There is no maximum dose	Possible gastrointestinal dysfunction, prevention of constipation is necessary

risk of interactions, especially pharmacokinetic ones. In patients with cardiovascular diseases, the daily dose of amitriptyline should not exceed 100 mg.

Of the SNRI class, venlafaxine and duloxetine are used. They are effective in the management of peripheral neuropathic pain, low back pain syndromes, brachial pain and fibromyalgia (level 1 evidence according to EBM) [23]. Drugs from the SNRI class are characterised by favourable safety profile compared with TCAs. Patients treated with SNRI may have elevated blood pressure. In about 15% of patients, sleep disorders may develop. SNRIs should be used with caution in patients with cardiovascular diseases.

12. Anticonvulsants

The mechanism of action of this class of drugs consists in the inhibition of neuronal hyperexcitability occurring in neuropathic pain, just as in epilepsy. Anticonvulsants are characterised by varied chemical composition and varied pharmacodynamic effects, which translates into their effectiveness in the management of neuropathic pain. The cellular mechanism of action of this class of drugs consists in the reduction in the concentration of sodium and/or calcium ions in neurons. The drugs potentate the processes of pre- and postsynaptic inhibition in the central nervous system structures.

Due to their high effectiveness and the safety profile in the management of neuropathic pain, drugs acting on the calcium channel α-2-δ subunit, i.e. pregabalin and gabapentin, are used most frequently. Despite similar mechanism of action, their effectiveness in the treatment of neuropathic pain may vary; lack of effectiveness of one drug can indicate the need for administration of another.

The effectiveness in the treatment of diabetic neuropathy and peripheral neuropathy has been shown for gabapentin (level 1 according to EBM) [21,23,30]. Treatment with gabapentin should be started with the lowest dose of 100 mg which should be systematically titrated upwards to 3600 mg/day until the expected analgesic effect is achieved. Typically, higher doses are effective. The most common adverse effect of gabapentin include excessive sedation, dizziness and gait instability.

The effectiveness of pregabalin was shown for postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, chronic post-surgical pain and lower back pain (level 1 according to EBM) [21,23,30]. The recommended dosage is 150–600 mg/day. Pregabalin does not interact with concomitant medications. Of the most common adverse effects, peripheral oedema, excessive sedation and dizziness should be listed.

What is characteristic for pregabalin is its linear pharmacokinetics which makes the relationship between the dose and the effectiveness more evident and predictable. Also, there are no clinically significant interactions with other drugs, which allows using it in patients with numerous comorbidities, unlike gabapentin. Pregabalin is the treatment of choice in elderly patients with neuropathic pain due to insignificant risk of inducing adverse reactions and in patients with cancer-related neuropathic pain.

Of other anticonvulsants, carbamazepine is used for the management of trigeminal neuralgia. Due to many years of experience, it is the first-line drug in this indication. The treatment should be started with low doses administered once or twice daily, and the doses should gradually be titrated upwards. In the case of no effectiveness or intense adverse effects after carbamazepine, oxcarbazepine at 300–3000 mg per day is recommended. In terms of potency of effect, 200 mg of carbamazepine is equivalent to 300 mg of oxcarbazepine. Adverse effects (liver damage, hyponatraemia) of oxcarbazepine are less common compared with carbamazepine.

Lamotrigine, an inhibitor of slow type IIA sodium channels, shows effectiveness in both peripheral neuropathic pain and central pain (level 1 according to EBM). Lamotrigine potentiates the effect of carbamazepine. However, when both drugs are combined, an increased risk of the Stevens-Johnson syndrome should be borne in mind. Treatment with lamotrigine is started with 50 mg on day 1, then the dose is increased to 100 mg on day 2, and 300 mg on day 3. On day 4, the dose of 400 mg is administered and then maintained as the therapeutic dose.

Valproic acid, which acts by the GABA-ergic system and by the inhibition of neuronal calcium and sodium channels, shows effectiveness in peripheral neuropathies, migraine and cluster headache and central pain (level 2 evidence according to EBM). Treatment is started with 300 mg, preferably administered at bedtime, and then the dose is increased every 3 days up to the maximum dose of 1500 mg/day. The most common adverse effects include sedation and hair loss. Hepatotoxicity may also occur, therefore long-term therapy necessitates monitoring of the liver function.

13. Opioid analgesics

Double-blind randomised clinical trials have shown that opioid analgesics have similar efficacy as gabapentin and TCAs in the treatment of neuropathic pain [5,21,23–25,30]. Weak opioids are less frequently used; usually in patients with moderate neuropathic pain or in elderly patients who are at a greater risk of developing adverse reactions to strong opioids. Due to its mechanism of action, tramadol may be treated as a weak opioid and recommended for the management of mild to moderate neuropathic pain and for the treatment of elderly patients [32].

The group of strong opioids recommended for the management of moderate to severe pain and available in Poland includes: morphine, oxycodone, fentanyl, buprenorphine and methadone. The choice of an opioid is not easy for several reasons. So far, no controlled clinical trials comparing various opioids have been conducted in patients with cancer-related neuropathic pain. Furthermore, published systematic reviews do not indicate unambiguously which opioid is the most effective in patients with neuropathic pain. Due to their mechanism of action, buprenorphine (antihyperalgesic effect) and methadone (in addition to the opioid component, the drug blocks NMDA receptors and increases the norepinephrine and serotonin concentration) appear to be the preferred opioids. In future, the use of tapentadol, which in addition to an opioid

component has an effect on the noradrenergic system, might also prove interesting [33].

Another option involves the concomitant use of two or more opioids, although no clear recommendations are available [34]. Typically, an opioid is combined with adjuvant analgesics, i.e. antidepressants and anticonvulsants. During treatment with opioids, possible adverse effects (e.g. constipation) should be borne in mind and prevented. Also, the consumption of medication should be monitored to prevent dependence, the risk of which is negligible if the treatment regimen is complied with.

14. Topical medication

Topical lidocaine acts primarily on voltage-gated pathological sodium channels in the damaged nerve, which initiate repeated ectopic excitations. The other mechanism of action of lidocaine is connected with the inhibition of the release of nociceptive mediators by keratinocytes, which account for 95% of epidermal cells and which are closely connected with nerve fibres. Lidocaine in the form of patches has an additional cooling effect on the skin (the patch is at the same time a hydrogel dressing) and provides disease-affected skin with mechanical protection [35,36].

5% lidocaine patches applied to the skin is recommended as the first-line treatment for localised peripheral neuropathic pain, alone or in combination with another first-line drug. NNT for 5% lidocaine in post-herpetic neuralgia is rated at 4.4 [5,30,37,38]. Published in 2009 metaanalysis of six databases (32 studies, 38 publications) showed that 5% lidocaine is effective in the management of post-herpetic neuralgia (level 1 evidence according to EBM), and in painful diabetic neuropathy its effectiveness is similar to that of amitriptyline, capsaicin, gabapentin and pregabalin [38]. However, the use of 5% lidocaine, compared with the above-mentioned drugs, is associated with fewer and less clinically significant adverse effects. The most common adverse effect is local skin irritation [39]. Furthermore, positive effects of 5% lidocaine have also been observed in intercostal neuralgia, chronic post-surgical pain (thoracotomy, mastectomy, inguinal hernia surgery, amputation) and *meralgia paraesthetica* [38].

Capsaicin is a highly selective vanilloid receptor agonist from the group of transient receptor potential vanilloid 1 (TRPV1) [40]. The mechanism of action of capsaicin consists in causing depletion of the neurotransmitter substance P from nerve fibre terminals. This results in reversible depletion of substance P supplies and reduction in pain transmission from the periphery to the higher layers of the central nervous system. However, the basic mechanism of action of 8% capsaicin primarily results from ion channels opening to calcium ions conjugated with TPRV1 receptor, which in turn results in defunctionalisation (atrophy) of primary nerve endings following reversible mitochondrial damage.

8% capsaicin patches have been available in Poland since 2009. The last review of the Cochrane Collaboration analysed the data from six studies involving 2073 participants comparing the results of 8% to the 0.04% (control group) topical capsaicin in post herpetic and HIV neuropathic pain. The highest rates of pain relief for 2–12 weeks were seen where capsaicin was applied for 60 min. The effectiveness of the high concentration of topical capsaicin is similar to the other drugs in chronic neuropathic pain [41].

15. NMDA receptor antagonists

Overexcitability of the NMDA receptor may be a cause of the central sensitisation phenomenon. To reduce the increased activity of the NMDA receptor, ketamine and dextromethorphan are used.

Ketamine is administered orally at 20–40 mg 4–6 times/day, epidurally at 30 mg or intravenously by a continuous infusion at 1–2 μg/kg b.w./min. Dextromethorphan, which may be used in both diabetic and post-herpetic neuropathy, is administered in 2–3 oral doses of 45 mg [23,30].

16. Management of neuropathic pain – recommendations

1. Pain management should be preceded by establishing the cause of neuropathic pain (e.g. diabetes mellitus) and starting an appropriate treatment (e.g. anti-diabetic treatment), if possible.
2. Prior to the initiation of pain treatment, relevant comorbidities (e.g. depression, cardiac or renal diseases) should be identified as they may constitute contraindications for treatment or necessitate analgesic dosage adjustment.
3. The patient should be informed about the diagnosis and treatment plan and should understand the need to hold realistic expectations about treatment effectiveness.
4. Specific neuropathic pain syndromes should be managed in accordance with the current recommendations related to these syndromes.
5. First-line drugs for neuropathic pain include:
   - TCAs or SNRIs (venlafaxine or duloxetine)
   - pregabalin or gabapentin
   - topical lidocaine
   - opioid analgesics or tramadol.
6. If the first-line treatment is effective (at least 50% pain reduction), it should be continued for adequate time. If the effectiveness is inadequate, another first-line drug should be added. If the first-line drug is not effective, it should be replaced with another first-line drug.
7. Lack of effectiveness of first-line drugs, used at adequate doses either alone or in combination, indicates the need for attempting treatment with second-line and third-line drugs.
8. Pharmacologic management should be complemented with non-pharmacologic modalities, if possible.
9. Treatment effectiveness should be assessed with appropriate frequency.

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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